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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Cernerud et al.
Serial No. : 10/622,055
Filed : July 17, 2003
Title : NEW COMPOUNDS

Art Unit : 1614
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TRANSMITTAL OF PRIORITY DOCUMENT UNDER 35 USC §119

Applicant hereby confirms his claim of priority under 35 USC §119 from the following application(s):

·Sweden Application No. 0202287-9 filed July 19, 2002

A certified copy of the application from which priority is claimed is submitted herewith.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13425-122001.

Respectfully submitted,

Date: November 12, 2003

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NEW COMPOUNDS

TECHNICAL FIELD

The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to processes for their preparation, as well as to the use of the compounds for the preparation of a medicament.

BACKGROUND ART

Many disorders and conditions of the central nervous system are influenced by the serotonergic neurotransmitter system. For example, serotonin (5-hydroxytryptamine; 5-HT) has been implicated in a number of disorders and conditions that originate in the central nervous system. The serotonin receptors are divided into seven main classes 5-HT_1- 5-HT_7. Additionally, the 5-HT_2 family of serotonin receptors is subdivided into the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptor subtypes. For reviews dealing with the classification and function characteristics of serotonin receptors, see for example: Hoyer, D. et al. Pharmacol. Rev. 1994, 46, 157-203; Saxena, P.R. Pharmacol. Ther. 1995, 66, 339-368; Barnes, N.M. et al. Neuropharmacol. 1999, 38, 1083-1152; Roth, B.L. et al. Pharmacol. Ther. 1998, 79, 231-257.

The 5-HT_{2A} receptor subtype is expressed in the human brain, including many cortical, limbic, and forebrain regions and is postulated to be involved in the modulation of higher cognitive and affective functions. The 5-HT_{2A} receptor subtype is also expressed on mature blood platelets where it mediates, in part, platelet aggregation, one of the initial steps in the process of vascular thrombosis. Several lines of evidence strongly implicate the 5-HT_{2A} receptor subtype in the etiology of such medical conditions as hypertension, thrombosis, migraine, vasospasm, ischemia, depression, anxiety, schizophrenia, obsessive-compulsive disorder, sexual function disorders, sleep disorders, and eating disorders, such as anorexia nervosa. They may further be effective in the lowering of intraocular pressure and may therefore be beneficial in treating glaucoma (cf. T. Mano et al. and H. Takaneka et al., Invest. Ophthalmol. Vis Sci. 1995, 36, 719 and 734, respectively). The compound

(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)-ethyl]-4-piperidinemethanol (also known as M-100907) has been shown to be a potent antagonist of human 5-HT_{2A} receptors and is described in WO 91/18602.

The 5-HT_{2A} receptor subtype has further been suggested to be involved in urological disorders such as diabetic nephropathy and urinary incontinence (diabetic nephropathy, see: Ishimura, E. et al. Nephron 1997, 76, 227-229; urinary incontinence, including coexisting diabetes, see: Kodama, M. et al. Int. J. Urol 2000, 7, 231-235 and Ichiyanagi, N. et al. J. Urol. 2002, 168, 303-307).

Compounds that have an effect on the 5-HT_{2A} receptor may therefore have a therapeutic potential in the treatment of disorders like those mentioned above.

INFORMATION DISCLOSURE

Various classes of compounds have been disclosed to act as antagonists at the 5-HT_{2A} receptor. For example, 4-aryl- or 4-heteroarylpiperazines such as those described in J. Med. Chem. 1991, 34, 2477- , Chem. Pharm. Bull. 1987, 35, 1919-, Bioorg. Med. Chem. Lett. 1997, 7, 1635-1638, and Arch. Pharm. 1995, 328, 659-666. Other compound classes reported to act as 5-HT_{2A} antagonists are disclosed in WO 0114332, WO 0004017, WO 0043362, WO 0107434, WO 0107435 and WO 0151469. A further class of 5-HT_{2A} antagonists is represented by the *N*-aralkyl-piperidine-methanol derivatives disclosed in US Patent no. 5,169,096, encompassing M-100907 mentioned above. The class of 5-HT_{2A} antagonists disclosed in U.S. Patent 5,169,096 are claimed to be useful in the treatment of a variety of disease states such as anorexia nervosa, variant angina, Raynaud's phenomenon, coronary vasospasms, hypertension, profylactic treatment of migraine, cardiovascular diseases such as hypertension, peripheral vascular disease, thrombotic episodes, cardiopulmonary emergencies and arrythmias, and has anesthetic properties. See also U.S. patents no. 4,877,798 (fibromyalgia); U.S. Patent no. 4,908,369 (insomnia); U.S. Patent no. 5,106,855 (glaucoma); U.S. Patent no. 6,004,980 (anxiety, Raynaud's phenomenon, cardiac arrythmia; extrapyramidal symptoms; drug abuse, anorexia, fibromyalgia); EP 337136 (treatment of extrapyramidal side effects associated with neuroleptic therapy). Psychotic illness such as schizophrenia and mania, among other indications are disclosed uses for M-100907 in U.S. Patent no. 5,134,149. The use of

M-100907 for the treatment of various developmental neurological disorders such as autism and attention deficit hyperactivity disorder is disclosed in WO 99/56750. The use of M-100907, and prodrugs thereof, for the treatment of symptoms of dementia, such as Alzheimer's disease, is disclosed in WO 01/89498. The use of M-100907 for the treatment of obsessive-compulsive disorders (OCD) is disclosed in U.S. Patent no. 5,618,824.

Ketanserin (3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-2,4(1*H*,3*H*)-quinazolinedione) is a 5-HT_{2A} antagonist that has been on certain markets for hypertension and is patented by Janssen in EP 13612 B. The use of ketanserin for the treatment of glaucoma is disclosed in EP 522226 (cf. Ophthalmologica 2001, 215, 419-423).

Sarpogrelate (butanedioic acid, mono[2-(dimethylamino)-1-[[2-[2-(3-methoxyphenyl)ethyl]phenoxy]methyl]ethyl] ester, MCI-9042; Anplag™), Mitsubishi, Japan, is a 5-HT_{2A} antagonist used for the treatment of thromboembolism in Japan and is disclosed in EP 72942 B. The use of sarpogrelate for the treatment of glaucoma is disclosed by Mitsubishi in EP 695545 and by Senju Pharmaceutical in CA 2144810. Sarpogrelate is also reported to have therapeutic potential in the treatment of diabetic complications (cf. Hotta, N. et al. Clin. Drug Invest. 1999, 18, 199-207; Kobori, S. et al. Int. Congr. Ser. 2000, 1209, 283-286).

The 5-HT_{2A} antagonist amperozide (4-(4,4-bis(4-fluorophenyl)butyl)-*N*-ethyl-1-piperazinecarboxamide) has been disclosed to possess antipsychotic properties and was first claimed by Pharmacia's subsidiary Ferrosan in the patent DE 02941880. Its use for the treatment of substance abuse is disclosed in the associated patent WO 09216211.

Ajinomoto is developing the 5-HT_{2A} antagonist and platelet aggregation inhibitor, AT-1015 (N-[2-{4-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidino}ethyl]-1-formyl-4-piperidinecarboxamide monohydrochloride monohydrate) for the potential treatment of thrombotic conditions (cf. European Journal of Pharmacology 2001, 433(2-3), 157-162).

Senju Pharmaceuticals has disclosed a series of 1,5-benzoxa-thiepine derivatives (e.g., methyl 7-methoxy-3-oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate) in US 5538974 and which are stated to be serotonin S_2 receptor antagonists and being useful for the treatment f glaucoma.

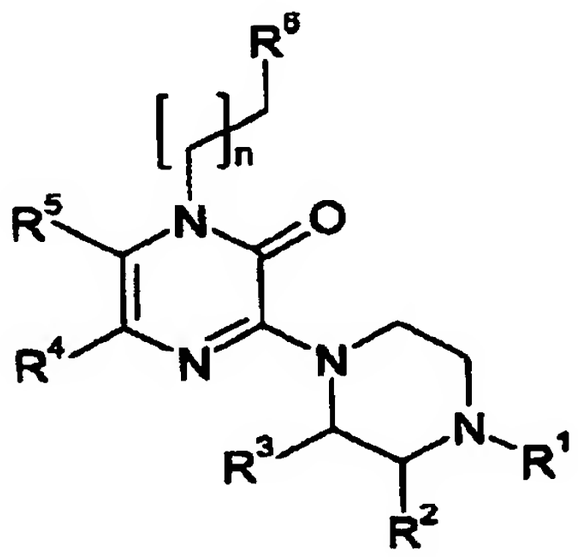
WO 00/64441 discloses, *inter alia*, a series of known 5-HT_{2A} antagonists (e.g., M-100907) for therapeutic or prophylactic treatment of disorders involving bronchoconstriction.

Some structurally related compounds to those of formula (I) in the present invention are disclosed in J. Med. Chem. 1981, 24, 93-101 and in GB 1,440,722. Particular compounds are 3-piperazin-1-yl-1*H*-quinoxalin-2-one, 1-methyl-3-piperazin-1-yl-1*H*-quinoxalin-2-one, 3-(4-methyl-piperazin-1-yl)-1*H*-quinoxalin-2-one, and 3-(1-piperazinyl)-1-[2-(dimethylamino)-ethyl]-2(1*H*)-quinoxalinone. 1-Benzyl-3-(4-methyl-piperazin-1-yl)-1*H*-quinoxalin-2-one is disclosed in Chem. Pharm. Bull. 1993, 41, 1832-1841.

WO 00/76984 discloses pyrazinyl ether compounds that bind to the 5-HT_{2C} receptor.

SUMMARY OF THE INVENTION

The present invention provides a new class of antagonists of the human 5-HT_{2A} receptor of general formula (I):



(I)

wherein

n represents 0, 1, 2, 3, or 4;

R^1 is H or C_{1-6}-alkyl, aryl-C_1-C_3-alkyl, heteroaryl-C_1-C_3-alkyl, 2-hydroxyethyl, methoxy-C_2-C_4-alkyl, C_1-C_4-alkoxycarbonyl; wherein any aryl or heteroaryl residue may be substituted with C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy or cyano;

R^2 and R^3 each, independently, represent H or CH_3;

R^4 and R^5 each, independently, represent H, halogen, methyl, or together with the ring, to which carbon atoms they are attached, form a 1*H*-quinoxalin-2-one nucleus; and

R^6 represents aryloxy, heteroaryloxy, arylthio, heteroarylthio, aryl-NH, heteroaryl-NH, aryl, or heteroaryl; wherein

any aryl or heteroaryl residue, alone or as part of another group, may be unsubstituted or substituted. Where substituted, one, two, three, four or five substituents may be present, preferably one or two for non-halogen substituents, and are independently selected from aryl, aryl-C_{1-2}-alkyl, arylcarbonyl, heteroaryl, heteroaryl-C_{1-2}-alkyl, heteroarylcarbonyl, aryloxy, heteroaryloxy, arylthio, heteroarylthio, arylamino, heteroarylamino, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyloxy, C_{3-6}-cycloalkylcarbonyl, C_{1-6}-alkyl, C_{2-6}-alkanoyl, C_{2-6}-alkynyl, C_{2-6}-alkenyl, or fluoro-C_{2-4}-alkyloxy, halogen, trifluoromethyl, nitro, cyano, trifluoromethoxy, trifluoromethylthio, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino, C_{1-4}-dialkylamino, hydroxy or oxo; wherein

any aryl or heteroaryl residue as substituents on aryl or heteroaryl, alone or as part of another group, in turn may be substituted in one, two, three, four or five positions, preferably one, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy, or cyano;

and pharmaceutically acceptable salts , hydrates, geometrical isomers, tautomers, optical isomers, *N*-oxides and prodrug forms thereof, with the provisos that:

R^2 and R^3 are not both CH_3;

when R^1, R^2, R^4 and R^5 are H and R^3 is H or CH_3, then R^6 is not 3-pyridyloxy, 6-methyl-2-nitro-3-pyridyloxy, or 2-chloro-3-pyridyloxy;

when n = 0, then R^6 is not aryloxy, heteroaryloxy, arylthio, heteroarylthio, aryl-NH or heteroaryl-NH; and

the compound of formula (I) is not 1-benzyl-3-(4-methyl-piperazin-1-yl)-1*H*-quinoxalin-2-one.

The compounds of the present invention may be regarded as structural isomers of compounds represented by formula (Ib), wherein X_1 is O, disclosed in WO 00/76984.

In case the compounds of formula (I) can be in the form of optical isomers, the invention comprises the racemic mixture as well as the individual enantiomers as such.

In case the compounds of formula (I) contain groups, which may exist in tautomeric forms, the invention comprises the tautomeric forms of the compounds as well as mixtures thereof.

In case the compounds of formula (I) can be in the form of geometrical isomers, the invention comprises the geometrical isomers as well as mixtures thereof.

According to another aspect, the invention provides the compounds according to formula (I) above for use in therapy in a number of disease states.

Still another aspect of the invention provides a pharmaceutical composition comprising a compound according to formula (I) above as the active ingredient, preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.

In yet another aspect, the invention provides a method for the treatment of a human or animal subject suffering from a serotonin-related disorder or condition, particularly 5-HT_{2A} receptor-related, such as angina, Raynaud's phenomenon, intermittent claudication, coronary or peripheral vasospasms, hypertension, fibromyalgia, thrombotic illness (including stroke), memory disorders, such as Alzheimer's disease; schizophrenia; obsessive-compulsive disorder; mood disorders; autism; anxiety disorders; depression disorders (including depression with coexisting diabetes), sexual function disorders, sleep disorders such as insomnia, pain; substance abuse; extrapyramidal symptoms (e.g., associated with neuroleptic drug therapy using drugs such as, for example, haloperidol and chlorpromazine); Parkinson's disease; glaucoma; urinary incontinence (including urinary incontinence with co-existing diabetes); menopausal and post-menopausal hot flushes; bronchoconstriction disorders; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; diabetic complications such as nephropathy, neuropathy and retinopathy.

Another aspect of the invention relates to the use of the compounds f formula (I) for the manufacture of a medicament for the treatment of a serotonin-related disorder or condition, particularly 5-HT_{2A} receptor-related, such as angina, Raynaud's phenomenon, intermittent claudication, coronary or peripheral vasospasms, hypertension, fibromyalgia, thrombotic illness (including stroke), memory disorders, such as Alzheimer's disease; schizophrenia; obsessive-compulsive disorder; mood disorders; autism; anxiety disorders; depression disorders (including depression with coexisting diabetes), sexual function disorders, sleep disorders such as insomnia, pain; substance abuse; extrapyramidal symptoms (e.g., associated with neuroleptic drug therapy using drugs such as, for example, haloperidol and chlorpromazine); Parkinson's disease; glaucoma; urinary incontinence (including urinary incontinence with co-existing diabetes); menopausal and post-menopausal hot flushes; bronchoconstriction disorders; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; diabetic complications such as nephropathy, neuropathy and retinopathy.

Finally a method for modulating 5-HT_{2A} receptor function is an aspect of the invention.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, a class of novel compounds that bind to the human 5-HT_{2A} receptor has been developed. The compounds act as receptor antagonists at the human 5-HT_{2A} receptor and may therefore be used for the treatment of serotonin-related disorders or conditions, particularly 5-HT_{2A} receptor-related.

First, the various terms used, separately and in combinations, in the above definition of the compounds having the general formula (I) will be explained.

The expression "C_{1-6} alkyl" refers to straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Particular C_{1-6} alkyl groups are methyl, ethyl, n-propyl, isopropyl, tert-butyl, and n-pentyl.

Derived expressions such as " C_{1-6} alkoxy" and " C_{1-6} alkylthio" are to be constructed accordingly.

The expression "C_{2-6} alkenyl" as used herein refers to straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl (2-propenyl), dimethylallyl and butenyl groups.

The expression "C_{2-6} alkynyl" as used herein refers to straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

The expression "C_{2-6} alkanoyl" as used herein refers to straight-chained and branched alkanoyl groups containing from 2 to 6 carbon atoms. Typical examples include acetyl, propionyl, n-butanoyl.

By "heteroatom" is meant nitrogen, oxygen, sulphur, and in heterocyclic rings (including heteroaromatic as well as saturated and partially saturated heterocyclic rings), also selenium.

The term "aryl" is intended to include aromatic rings (monocyclic or bicyclic) having from 6 to 10 ring carbon atoms, such as phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl. The aryl group can be linked to the remainder of the molecule via a carbon atom in any ring.

The term "heteroaryl" means a mono- or bicyclic aromatic ring system, only one ring need be aromatic, and the said heteroaryl moiety can be linked to the remainder of the molecule via a carbon or nitrogen atom in any ring, and having from 5 to 10 ring atoms (mono- or bicyclic), in which one or more of the ring atoms are other than carbon, such as nitrogen, sulphur, oxygen and selenium. Examples of such heteroaryl rings are pyrrole, imidazole, thiophene, furan, thiazole, isothiazole, thiadiazole, oxazole, isoxazole, oxadiazole, pyridine, pyrazine, pyrimidine, pyridazine, pyrazole, triazole, tetrazole, chroman, isochroman, coumarin, quinoline, quinoxaline, isoquinoline, phthalazine, cinnoline, quinazoline, indole, isoindole, indoline, isoindoline, benzothiophene, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, benzoxazole, 2H-chromene, benzisoxazol, 1,3-benzooxathiole, 2,1,3-benzoxadiazole, benzothiazole, 2,1,3-benzothiadiazole, 2,1,3-benzoselenadiazole, benzimidazole, indazole, 2,3-dihydro-1,4-benzodioxine, 1,3-benzodioxole, 1,2,3,4-tetrahydroquinoline, 3,4-dihydro-2*H*-1,4-benzoxazine, 1,5-naphthyridine, 1,8-naphthyridine, 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine, and 2,3-dihydro-1,4-benzoxathiine. If a bicyclic aryl or heteroaryl ring is substituted, it may be substituted in any ring.

Halogen includes fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine. Fluorine is a preferred halogen when it is part of R^6 as substituent.

Where it is stated above that aryl and heteroaryl residues may be substituted (in one or more positions), this applies to aryl and heteroaryl *per se* as well as to any combined groups containing aryl or heteroaryl residues, such as heteroaryl-C_{1-3}-alkyl and arylcarbonyl, etc.

The term "*N*-oxides" means that one or more nitrogen atoms, when present in a compound, are in *N*-oxide form (N→O).

The term "prodrug forms" means a pharmacologically acceptable derivative, such as a carbamate or an amide, which derivative is biotransformed in the body to form the active drug. Reference is made to Goodman and Gilman's, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15.

"Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, malic acid, oxalic acid, toluenesulphonic acid, methanesulphonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like.

The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives or carriers may be present.

"Extrapyramidal symptoms" are symptoms that may manifest upon administration of neuroleptic drugs. The symptoms include a parkinsonian-like syndrome wherein the patient experiences muscular rigidity and tremors. Some experience akathesia and acute dystonic reactions.

The expressions "*N*-*t*-BOC derivative" or "*N*-*t*-BOC intermediate" as mentioned in the Exemplary Section, refers to a compound of formula (I) where R^1 is *t*-butoxycarbonyl (*t*-BOC).

Preferred embodiments of the invention are compounds of formula (I) wherein

n = 1;

R^1, R^2, R^3, R^4 and R^5 each are H; and

R^6 is phenoxy, where the phenyl ring of the said phenoxy group may be unsubstituted or substituted. Where substituted, one, two, three, four or five substituents may be present, which may be the same or different, preferably one or two for non-halogen substituents. Examples of preferred substituents on the said R^6 phenoxy group are independently selected from halogen, 2-propenyl, C_1-C_6-alkyl, C_1-C_6-alkoxy, trifluoromethyl, phenyl, phenoxy, benzoyl, and C_3-$_6$-cycloalkyl; wherein any of the phenyl, phenoxy or benzoyl in turn may be substituted in one, two or three positions, preferably by halogen. Even more preferably, R^6 is substituted with 2,4,5-trifluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2,4-difluorophenoxy, 2,3,4-trifluorophenoxy, 2-fluoro-4-chlorophenoxy, 4-bromophenoxy, and 2,3-dichlorophenoxy.

In another preferred embodiment of the invention is a compound of formula (I) in which

n = 1;

R^1 is C_1-C_6-alkyl;

R^2, R^3, R^4 and R^5 each are H; and

R^6 is 2,4,5-trifluorophenoxy.

In still another preferred embodiment of the invention is a compound of formula (I) in which

n = 1;

R^1, R^2, R^3, R^4 and R^5 each are H; and

R^6 is 2-oxo-1,3-benzoxathiol-6-yloxy.

In yet another preferred embodiment of the invention is a compound of formula (I) in which

n = 0;

R^1, R^2, R^3, R^4 and R^5 each are H; and

R^6 is phenyl, where the said phenyl may be substituted with halogen, preferably fluorine, in one, two, three, four or five positions. Even more preferably, R^6 represents 2,4,5-trifluorophenyl.

Preferred compounds of the general formula (I) above are:

- 1-[2-(2-fluoro-4-nitrophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-{2-[(2-oxo-2*H*-chromen-7-yl)oxy]ethyl}-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 3-(1-piperazinyl)-1-[2-(2,4,5-trifluorophenoxy)ethyl]-2(1*H*)-pyrazinone,
- 3-(1-piperazinyl)-1-[2-(2,3,5,6-tetrafluorophenoxy)ethyl]-2(1*H*)-pyrazinone,
- 1-[2-(2,3,4,5,6-pentafluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-chloro-2-fluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-cyanophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-cyclopentylphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(1,2-benzisoxazol-3-yloxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-methoxyphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-*n*-butyloxyphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-([1,1'-biphenyl]-3-yloxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 3-(1-piperazinyl)-1-[2-(2,3,4-trifluorophenoxy)ethyl]-2(1*H*)-pyrazinone,
- 1-[2-(2,3-dichlorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(1,3-benzodioxol-5-yloxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,4-difluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-{2-[(2-oxo-1,3-benzoxathiol-6-yl)oxy]ethyl}-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-hydroxyphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 3-(1-piperazinyl)-1-[2-(6-quinoxalinyloxy)ethyl]-2(1*H*)-pyrazinone,

- 1-{2-[3-(*N*,*N*-dimethylamino)phenoxy]ethyl}-3-(1-piperazinyl)-pyrazin-2(1*H*)-one,
- 3-(1-piperazinyl)-1-{2-[3-(trifluoromethyl)phenoxy]ethyl}-2(1*H*)-pyrazinone,
- 1-[2-(3-fluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-nitrophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3,5-difluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(phenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,6-difluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2-cyanophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-trifluoromethylphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-bromophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-{4-phenoxy-(phenoxy)}ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-fluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-isopropylphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-{(4-allyl-2-methoxy)phenoxy}ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,6-difluorophenoxy)ethyl]-3-(3-methyl-1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-trifluoromethylphenoxy)ethyl]-3-(3-methyl-1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-bromophenoxy)ethyl]-3-(3-methyl-1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-(2,4,5-trifluorobenzyl)-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[3-(2,4,5-trifluorophenyl)propyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,4,5-trifluorophenoxy)ethyl]-3-(4-*n*-butyl-1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,4,5-trifluorophenoxy)ethyl]-3-(4-methyl-1-piperazinyl)-2(1*H*)-pyrazinone,

- 1-[2-(2,4,5-trifluorophenoxy)ethyl]-3-(4-isopropyl-1-piperazinyl)-2(1*H*)-pyrazinone, and
- 1-[2-(3-benzoylphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone.

and their pharmacologically acceptable salts and solvates.

As mentioned above, the compounds of the present invention are useful for the treatment, including prophylactic treatment, of serotonin-related, especially 5-HT_{2A} receptor-related, disorders and conditions, in a human being or in an animal, including e.g. pets, such as angina; Raynaud's phenomenon; intermittent claudication; coronary or peripheral vasospasms; hypertension; fibromyalgia; thrombotic illness, including stroke; memory disorders, such as Alzheimer's disease; schizophrenia; obsessive-compulsive disorder; mood disorders; autism; anxiety disorders; depression disorders, including depression with coexisting diabetes; sexual function disorders; sleep disorders such as insomnia; pain; substance abuse; extrapyramidal symptoms (e.g., associated with neuroleptic drug therapy using drugs such as, for example, haloperidol and chlorpromazine); Parkinson's disease; glaucoma; urinary incontinence,including urinary incontinence with co-existing diabetes; menopausal and post-menopausal hot flushes; bronchoconstriction disorders; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; diabetic complications such as nephropathy, neuropathy and retinopathy.

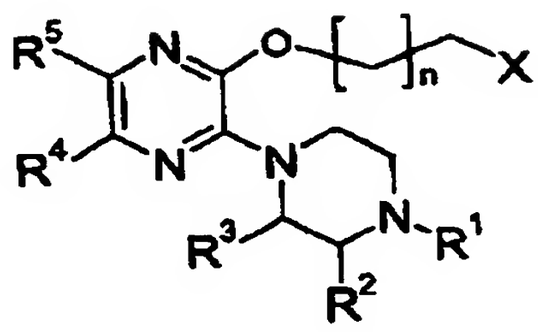
The compounds of the present invention in radiolabelled form may be used as a diagnostic agent.

PROCESSES FOR PREPARATION

This invention also relates to methods of making compounds of any formulae delineated herein comprising reacting any one or more of the compounds or formulae delineated herein including any processes delineated herein.

In one aspect, the invention is a method of making a compound of formula (I) delineated herein. The compounds of general formula (I) above may be prepared by, or in analogy with, conventional methods, and especially according to or in analogy with the following methods:

Compounds of formula (I) are prepared by reacting a compound of the structural formula (II):



(II)

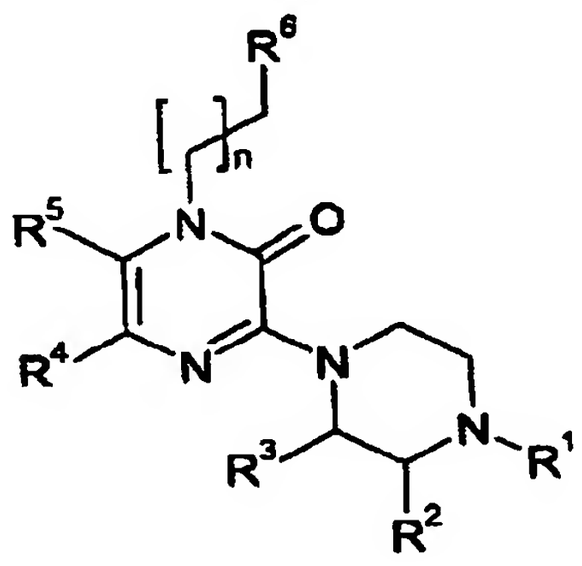
wherein

n represents 0, 1, 2, 3 or 4;

X is OH; and

R^1, R^2, R^3, R^4 and R^5 are as defined for formula (I);

with 1 to 10 molar equivalents of an appropriate phenol or thiophenol under Mitsunobu conditions (cf. Org. Reactions 1992, 42, 335-656 and Tetrahedron Lett. 1995, 36, 3789-3792) to produce a compound of formula (I):



(I)

wherein

R^1, R^2, R^3, R^4, R^5 and n are as defined for formula (I);

R^6 is selected from aryloxy, heteroaryloxy, arylthio, heteroarylthio, aryl-NH, or heteroaryl-NH; wherein

any aryl or heteroaryl residue, alone or as part of another group, may be unsubstituted or substituted. Where substituted, one, two, three, four or five substituents may be present, preferably one or two for non-halogen substituents, and are independently selected from aryl, aryl-C_{1-2}-alkyl, arylcarbonyl, heteroaryl, heteroaryl-C_{1-2}-alkyl, heteroarylcarbonyl, aryloxy.

heteroaryloxy, arylthi , heteroarylthio, arylamino, heteroarylamino, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyloxy, C_{3-6}-cycloalkylcarbonyl, C_{1-6}-alkyl, C_{2-6}-alkanoyl, C_{2-6}-alkynyl, C_{2-6}-alkenyl, or fluoro-C_{2-4}-alkyloxy, halogen, trifluoromethyl, nitro, cyano, trifluoromethoxy, trifluoromethylthio, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino, C_{1-4}-dialkylamino, hydroxy or oxo;

wherein

any aryl or heteroaryl residue as substituents on aryl or heteroaryl, alone or as part of another group, in turn may be substituted in one or more positions, preferably one, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy, or cyano.

Typically, the said Mitsunobu reaction is carried out in the presence of diethyl azodicarboxylate (DEAD) or 1,1'-azobis(*N*,*N*-dimethylformamide (TMAD), preferably TMAD, and triphenylphosphine or tri-*n*-butylphosphine, preferably triphenylphosphine, in a solvent such as *N*,*N*-dimethylformamide (DMF), dichloromethane or tetrahydrofuran (THF), especially DMF, or in a suitable mixture of solvents, such as THF:DMF, at -25 to 50 °C, typically at room temperature, for 1-48 hours.

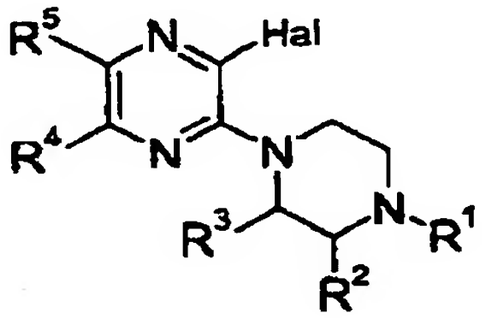
For compounds of formula (I) where R^1 is H, R^1 in the corresponding intermediate of formula (II) is a suitable protecting group, preferably *tert*-butoxycarbonyl (*t*-BOC) or trityl.

The intermediates of formula (II) may be prepared according to the methodology described in WO 00/76984.

The method described above producing a compound of formula (I) from a compound of formula (II) may produce a mixture of structural isomers containing the desired compound of formula (I) according to the current invention and the corresponding structural isomer of formula (Ib) disclosed in WO 00/76984. The ratio of the two structural isomers may vary depending on the experimental conditions used. These compounds may be conveniently separated by conventional techniques including chromatography, such as column chromatography on silica gel or preparative HPLC. The identity of the individual structural isomers may be established by spectroscopic techniques such as nuclear magnetic resonance (NMR)

spectroscopy, including proton and carbon NMR (^{1}H NMR and ^{13}C NMR) spectroscopy, and infrared spectroscopy (IR).

Alternatively, the compounds of formula (I) can also be prepared by reacting a compound of formula (IV),



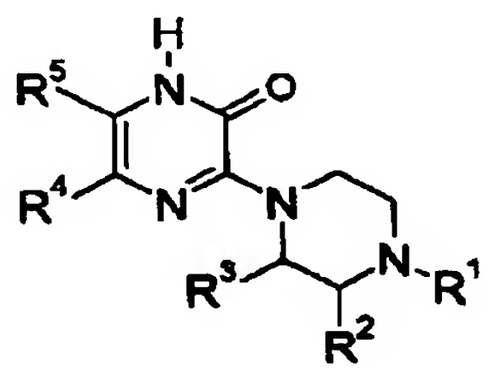
(IV)

wherein

Hal is halogen, typically chlorine; and

R^1, R^2, R^3, R^4, and R^5 are as defined for formula (I);

with an alkali metal or alkaline earth metal basic salt , eg., a hydroxide or carbonate such as NaOH or K_2CO_3, in aqueous media, such as water:dimetyl sulfoxide (DMSO), at 25 to 150 °C, to produce a compound of formula (V),



(V)

wherein R^1, R^2, R^3, R^4, and R^5 are as defined for formula (I), followed by *N*-alkylation of the compound of formula (V) by reaction with a compound of formula (VI),

(VI)

wherein

n is 0, 1, 2, 3 or 4;

Y is a suitable leaving group such as mesylate, tosylate, chlorine, bromine or iodine; and

R^6 represents aryloxy, heteroaryloxy, arylthio, heteroarylthio, aryl-NH, heteroaryl-NH, aryl, or heteroaryl; wherein

any aryl or heteroaryl residue, alone or as part f another group, may be unsubstituted or substituted. Where substituted, one, two, three, four or five substituents may be present, preferably one or two for non-halogen substituents, and are independently selected from aryl, aryl-C_{1-2}-alkyl, arylcarbonyl, heteroaryl, heteroaryl-C_{1-2}-alkyl, heteroaylcarbonyl, aryloxy, heteroaryloxy, arylthio, heteroarylthio, arylamino, heteroarylamino, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyloxy, C_{3-6}-cycloalkylcarbonyl, C_{1-6}-alkyl, C_{2-6}-alkanoyl, C_{2-6}-alkynyl, C_{2-6}-alkenyl, or fluoro-C_{2-4}-alkyloxy, halogen, trifluoromethyl, nitro, cyano, trifluoromethoxy, trifluoromethylthio, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino, C_{1-4}-dialkylamino, hydroxy or oxo;

wherein

any aryl or heteroaryl residue as substituents on aryl or heteroaryl, alone or as part of another group, in turn may be substituted in one or more postions, preferably one, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy, or cyano;

typically in the presence of a base such as an alkali metal hydride, such as sodium hydride, or sodium or potassium *tert*-butoxide (*t*-BuONa or *t*-BuOK), or potassium carbonate or caesium carbonate or the like in a suitable solvent such as THF, dioxane, diglyme, 1,2-dimethoxyethane, or acetonitrile, suitably at an elevated temperature, typically the reflux temperature of the solvent employed. The said *N*-alkylation reaction may be carried out in the presence of sodium iodide or potassium iodide in cases where Y in formula (VI) is other than iodine.

For compounds of formula (I) where R^1 is H, R^1 in the intermediate of formula (V) is a suitable protecting group, preferably *tert*-butoxycarbonyl (*t*-BOC) or trityl.

The intermediates of formula (IV) may be prepared according to the methodology described in WO 00/76984.

When R^1 is a nitrogen protecting group, such as *tert*-butoxycarbonyl (*t*-BOC) or trityl, the subsequent *N*-deprotection is carried out by conventional methods such as those described in Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

An obtained compound of formula (I) above may be converted to another compound of formula (I) by methods well known in the art.

The process that is described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. A pharmaceutically acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Examples of addition salt forming acids are maleic acid, malic acid, fumaric acid, succinic acid, methanesulfonic acid, acetic acid, oxalic acid, benzoic acid, hydrochloric acid, sulphuric acid, phosphoric acid, and the like.

The compounds of formula (I) may possess one or more chiral carbon atoms, and they may therefore be obtained in the form of optical isomers, e.g. as a pure enantiomer, or as a mixture of enantiomers (racemate) or as a mixture containing diastereomers. The separation of mixtures of optical isomers to obtain pure enantiomers is well known in the art and may, for example, be achieved by fractional crystallization of salts with optically active (chiral) acids or by chromatographic separation on chiral columns.

The necessary starting materials for preparing the compounds of formula (I) are either known or may be prepared in analogy with the preparation of known compounds.

In accordance with the present invention, the compounds of formula (I), in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of formula (I) in association with compatible pharmaceutically acceptable carrier materials, or diluents, as are well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous, subcutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmacologically active

agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavoring agents, buffers, and the lik .

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, pills, capsules, powders, syrups, elixirs, dispersable granules, cachets, suppositories and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, sprays, e.g. a nasal spray, transdermal preparations, e.g. patches, and the like.

As mentioned above, the compounds of the invention may be used for the treatment of serotonin-related, especially 5-HT_{2A} receptor-related, disorders and conditions in a human being or an animal, such as angina, Raynaud's phenomenon, intermittent claudication, coronary or peripheral vasospasms, hypertension, fibromyalgia, thrombotic illness (including stroke), memory disorders, such as Alzheimer's disease; schizophrenia; obsessive-compulsive disorder; mood disorders; autism; anxiety disorders; depression disorders (including depression with coexisting diabetes), sexual function disorders, sleep disorders such as insomnia, pain; substance abuse; extrapyramidal symptoms (e.g., associated with neuroleptic drug therapy using drugs such as, for example, haloperidol and chlorpromazine); Parkinson's disease; glaucoma; urinary incontinence (including urinary incontinence with co-existing diabetes); menopausal and post-menopausal hot flushes; bronchoconstriction disorders; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; diabetic complications such as nephropathy, neuropathy and retinopathy.

The dose level, frequency of dosage, mode of administration, of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

The invention will now be illustrated with the following examples, which however, are for illustrative purposes are not intended to limit the scope of the invention.

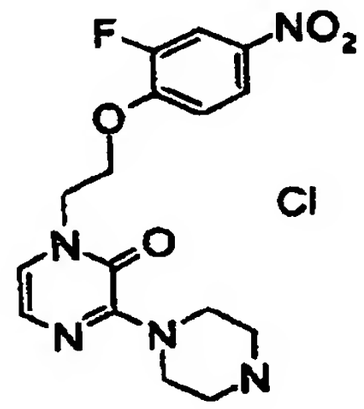
EXAMPLES

Experimental methods

NMR spectra were recorded on a Bruker DPX 400, Bruker DRX 500, Jeol 270 or on a Varian Unity Inova 400 spectrometer. Column chromatography was performed on Silica gel 60 (230-400 mesh, E. Merck). The preparative HPLC purifications were performed on a YMC OPS-AQ CombiPrep column (50 x 20 mm, i.d., 5 µm particle size, 120 Å), using various gradients of acetonitrile-water containing 0.1% TFA as eluent at a flow rate of 30 mL/min, using a LC/MS Gilson-Finnigan instrument equipped with Gilson pumps, a Dynamax UV-1 detector and a Finnigan Mass detector. Analytical reversed-phase HPLC analyses were carried out on a ACE C8 column (50 x 4.6 mm) using various gradients of acetonitrile-water, containing 0.005 M ammonium acetate, at a flow rate of 1 mL/min, using a Waters ZQ LC-MS setup. "Speed-vac" refers to a Speed-vac Plus SC250DDA or a Gene-vac DD-4. The accurate mass analyses were determined on a Micromass LCT instrument using electrospray ionisation. The elemental analyses were performed by MikroKemi AB, Uppsala, Sweden or on an Elementar Vario EL instrument at Biovitrum AB, Stockholm, Sweden, and reported results were within ±0.4% of the theoretical values. Melting points, when given, were obtained on a Büchi Meltingpoint B-545, Electrothermal IA 9000, or a Gallenkamp MPD350 apparatus and are uncorrected. The intermediate 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)- pyrazinyloxy]ethanol was prepared as described in WO 00/76984.

EXAMPLE 1

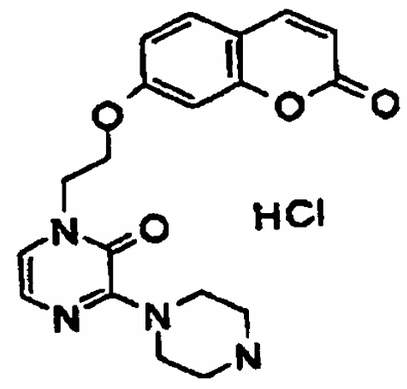
1-[2-(2-Fluoro-4-nitrophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Hydrochloride.



2-Fluoro-4-nitrophenol (732 mg, 4.66 mmol), 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (1.375 g, 4.240 mmol) and triphenylphosphine (1.22 g, 4.66 mmol) were dissolved in THF (8 mL) and 1,1'-azobis(*N*,*N*-dimethylformamide (TMAD; 802 mg, 4.66 mmol) was added in three portions. The reaction mixture was stirred at room temperature overnight and then centrifugated. The supernatant was concentrated in vacuo. The residue was dissolved in ethyl acetate (EtOAc) and washed with 5% $NaHCO_3$ and brine. The organic layer was concentrated in vacuo and the residue purified by flash-chromatography using EtOAc/toluene (4:6) as eluent to give 451 mg (23 %) of the title compound as its *N*-*t*-BOC derivative. The *N*-*t*-BOC intermediate (440 mg, 0.949 mmol) was treated with trifluoroacetic acid (TFA)/CH_2Cl_2/H_2O (36:60:4, 3.6 mL) for 45 min. The solution was concentrated in vacuo and the residue precipitated with ether. This material was dissolved in 50% aqueous MeOH (15 mL) and passed through an anion exchange resin (Dowex-1 X8, Cl^-, 4 g) eluting with 50% aqueous MeOH. Evaporation of the solvent in vacuum gave the title compound. Yield 364 mg (96 %), mp 105-108 °C; MS-EI *m/z* 363 $(M)^+$. Anal. ($C_{16}H_{18}N_5O_4F \cdot 1.1\ HCl \cdot 0.2\ H_2O$) C, H, N.

EXAMPLE 2

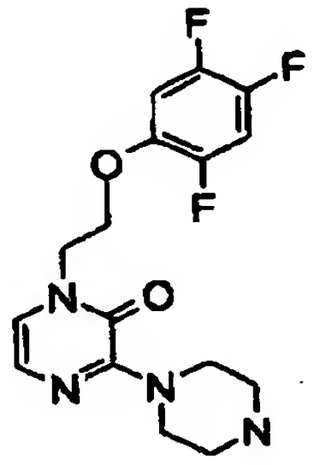
1-{2-[(2-Oxo-2H-chromen-7-yl)oxy]ethyl}-3-(1-piperazinyl)-2(1H)-pyrazinone, Hydrochloride.



Diethyl azodicarboxylate (DEAD; 0.63 mL, 4.0 mmol) was added over 20 min to a stirred mixture of 7-hydroxycoumarin (713 mg, 4.40 mmol), 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (1.29 g, 4.00 mmol) and triphenylphosphine (1.05 g, 4.00 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature overnight. Removal of solvent in vacuum and purification of the residue by repeated chromatography on silica gel using EtOAc/toluene and CH_2Cl_2/MeOH (96:4) as eluents, respectively, gave 871 mg (46%) of the title compound as its *N*-*t*-BOC derivative. The *N*-*t*-BOC intermediate (800 mg, 1.71 mmol) was treated with TFA/CH_2Cl_2/H_2O (40:55:5; 4.2 mL) for 70 min. The solution was evaporated and the residue precipitated with ether. This material (843 mg) was dissolved in 50% aqueous MeOH (10 mL) and passed through an anion exchange resin (Dowex-1 X8, Cl^-, 5 g) eluting with 50% aqueous MeOH. The resulting hydrochloride salt of the title compound was further purified by chromatography on LiChroprep RP-18 (Merck) reversed phase silica gel (5 x 2.5 cm) eluting with 25% CH_3CN in 0.02 M HCl. The product-containing fractions were pooled, concentrated in vacuo and freeze-dried to furnish 600 mg (85%) of the title compound. MS-EI *m/z* 368 $(M)^+$. Anal. ($C_{19}H_{20}N_4O_4 \cdot HCl \cdot 0.7\ H_2O$) C, H, N.

EXAMPLE 3

3-(1-Piperazinyl)-1-[2-(2,4,5-trifluorophenoxy)ethyl]-2(1H)-pyrazinone, Hydrochloride.

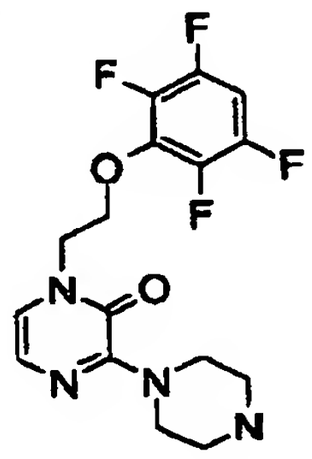


Cl

2,4,5-Trifluorophenol (533 mg, 3.60 mmol), 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (972 mg, 3.00 mmol), TMAD (619 mg, 3.60 mmol) and polymer-bound triphenylphosphine (Fluka) (1.2 g, 3.6 mmol) were shaken in CH_2Cl_2 (10 mL) under nitrogen for about 21 h. The polymer was filtered off and washed with CH_2Cl_2. The solvent was evaporated and the residue was dissolved in $CHCl_3$ and washed with 1 M Na_2CO_3 and brine. Removal of solvent in vacuo and purification of the residue by column chromatography on silica gel using $CHCl_3$ → $CHCl_3$/MeOH (98:2) as eluent gave 791 mg (58%) of the title compound as its *N*-*t*-BOC derivative. The *N*-*t*-BOC intermediate (700 mg, 1.54 mmol) was treated with TFA/CH_2Cl_2/H_2O (42:53:5; 4 mL) and kept at room temperature for 50 min with stirring. The solution was concentrated and the residue precipitated with MeOH/ether. This material was dissolved in 50% aqueous MeOH and passed through an anion exchange resin (Dowex-1 X8, Cl^-, 4 g) eluting with 50% aqueous MeOH. Evaporation of the solvent in vacuum gave the title compound. Yield: 513 mg (85%); mp 193-195 °C; MS-EI *m/z* 354 $(M)^+$; HRMS *m/z* calcd for $C_{16}H_{17}F_3N_4O_2$ $(M)^+$ 354.1304, found 354.1301. Anal. ($C_{16}H_{17}F_3N_4O_2 \cdot HCl$) C, H, N.

EXAMPLE 4

3-(1-Piperazinyl)-1-[2-(2,3,5,6-tetrafluorophenoxy)ethyl]-2(1H)-pyrazinone, Hydrochloride.



Cl

2,3,5,6-Tetrafluorophenol (556 mg, 3.35 mmol), 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (1.01 g, 3.10 mmol) and triphenylphosphine (813 mg, 3.10 mmol) were dissolved in THF (10 mL) and TMAD (533 mg, 3.10 mmol) was added in three portions over 50 min. The reaction mixture was stirred at room temperature overnight. A small amount of a white precipitate was filtered off. The filtrate was evaporated, redissolved in ether and filtered again. The filtrate was washed with 5% $NaHCO_3$ and brine, concentrated in vacuo, and the residue purified by flash chromatography using EtOAc/toluene (3:7 followed by 1:4) as eluent. This gave 584 mg (40%) of the title compound as its *N*-*t*-BOC derivative. The *N*-*t*-BOC intermediate (568 mg, 1.20 mmol) was treated with TFA/CH_2Cl_2/H_2O (42:53:5; 3.1 mL) at room temperature for 50 min with stirring. The solution was evaporated and the residue precipitated with MeOH-ether. This product was dissolved in 50% aqueous MeOH and passed through an anion exchange resin (Dowex-1 X8, Cl^-, 4 g) eluting with 50% aqueous MeOH. Evaporation of the solvent in vacuum gave the title compound. Yield: 453 mg (92%); mp 196-198 °C (dec.); MS-EI *m/z* 372 $(M)^+$; HRMS *m/z* calcd for $C_{16}H_{16}F_4N_4O_2$ $(M)^+$ 372.1209, found 372.1196. Anal. ($C_{16}H_{16}F_4N_4O_2$ · HCl) C, H, N.

EXAMPLE 5

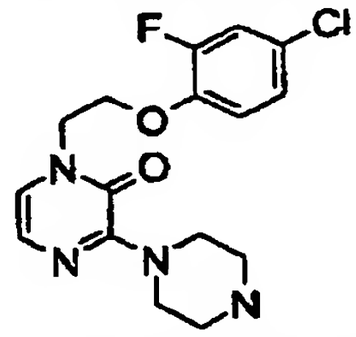
1-[2-(2,3,4,5,6-Pentafluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Hydrochloride.

Cl

Pentafluorophenol (608 mg, 3.30 mmol), 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (1.01 g, 3.10 mmol) and triphenylphosphine (813 mg, 3.10 mmol) were dissolved in THF (5 mL) and TMAD (533 mg, 3.1 mmol) was added in three portions. The reaction mixture was stirred at room temperature overnight. A small amount of a white precipitate was filtered off. The filtrate was concentrated in vacuo and the residue was dissolved in ether, washed with 5% $NaHCO_3$ and brine. Removal of solvent in vacuo and purification of the residue by flash chromatography using toluene/EtOAc (3:7 followed by 1:4) as eluent gave 332 mg (22 %) of the title compound as its *N*-*t*-BOC derivative. This material (0.677 mmol) was treated with TFA/CH_2Cl_2/H_2O, (42:53:5; 1.74 mL) for 1 h. The solution was evaporated and the residue precipitated with MeOH/ether. This product was dissolved in 50% aqueous MeOH and passed through an anion exchange resin (Dowex-1 X8, Cl^-, 4 g) eluting with 50% aqueous MeOH. Evaporation of the solvent in vacuum gave the title compound. Yield: 275 mg (92%). MS-EI *m/z* 390 $(M)^+$. HRMS *m/z* calcd for $C_{16}H_{15}F_5N_4O_2$ $(M)^+$ 390.1115, found 390.1106. Anal. ($C_{16}H_{15}F_5N_4O_2$ · HCl) C, H, N.

EXAMPLE 6

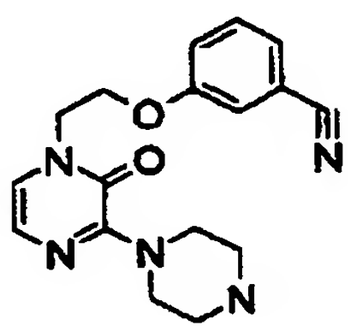
1-[2-(4-Chloro-2-fluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



1,1'-Azobis(*N,N*-dimethylformamide (TMAD; 0.217 g, 1.26 mmol) was added to a stirred mixture of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.324 g, 1.00 mmol), triphenylphosphine (0.324 g, 1.23 mmol) and 4-chloro-fluorophenol (0.217 g, 1.48 mmol) in THF (1 mL) at room temperature. After 2 h, the reaction mixture was concentrated and the crude *N*-*t*-BOC derivative of the title compound was *N*-deprotected with TFA/CH_2Cl_2/H_2O (45:50:5). Purification by silica gel chromatography using EtOAc/toluene (4:6) as eluent gave the title compound as a yellow oil (0.123 g, 35% yield). HRMS *m/z* calcd for $C_{16}H_{18}ClFN_4O_2$ $(M)^+$ 352.1102, found 352.1098.

EXAMPLE 7

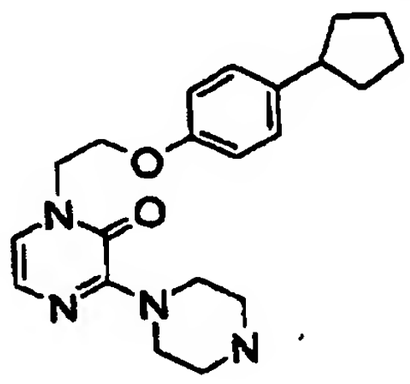
1-[2-(3-Cyanophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



The title compound was prepared according to the procedure described in Example 6 starting from 3-cyanophenol (0.149 g, 1.25 mmol). This gave 115 mg (35%) of the title compound as a yellow solid; mp 49-52 °C. HRMS *m/z* calcd for $C_{17}H_{19}N_5O_2$ $(M)^+$ 325.1539, found 325.1549.

EXAMPLE 8

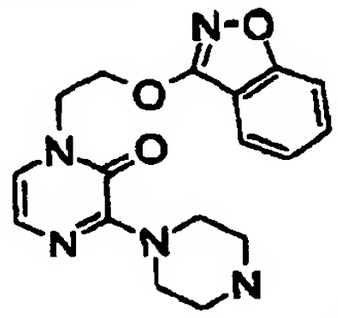
1-[2-(4-Cyclopentylphenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



The title compound was prepared according to the procedure described in Example 6 starting from 4-cyclopentylphenol (0.203 g, 1.25 mmol). This gave 30 mg (8%) of the title compound as a yellow oil (30 mg, 8% yield). HRMS *m/z* calcd for $C_{21}H_{28}N_4O_2$ $(M)^+$ 368.2212, found 368.2193

EXAMPLE 9

1-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Dihydrochloride.

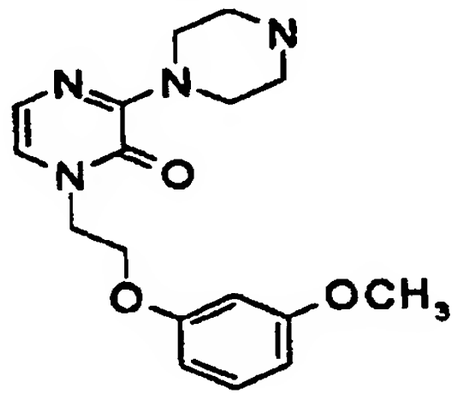


HCl
HCl

The title substance was prepared by dissolving 3-hydroxybenzisoxazole (0.324 g, 1.0 mmol), tri-*n*-butylphosphine (PBu_3; 0.360 mL, 1.46 mmol), 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.324 g, 1.00 mmol) in DMF (1 mL) and adding 1,1'-azobis(*N*,*N*-dimethylformamide (TMAD; 0.215 g, 1.25 mmol). The reaction was heated in a Labwell microwave reactor, 1 min at 75W. The *N*-*t*-BOC derivative of the title compound was purified by silica gel chromatography using MeOH/$CHCl_3$ (5:95) as eluent. The subsequent *N*-deprotection was carried out using TFA/CH_2Cl_2/H_2O (45:50:5). The title product was isolated as a yellow solid. Yield: 0.085 g (20%); mp 174-176°C. HRMS *m/z* calcd for $C_{17}H_{19}N_5O_3$ $(M)^+$ 341.1488, found 341.1496.

EXAMPLE 10

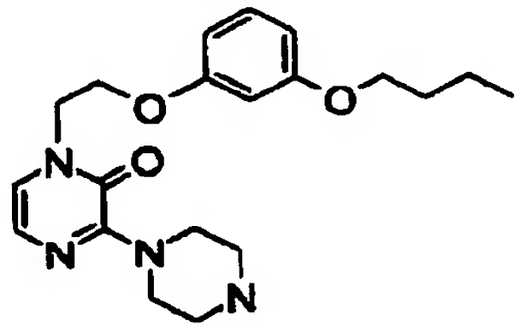
1-[2-(3-Methoxyphenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



TMAD (0.060 g, 0.35 mmol) was dissolved in THF (1 mL) and DMF (0.5 mL) and the solution added dropwise to a mixture of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.100 g, 0.310 mmol), triphenylphosphine (0.092 g, 0.35 mmol) and 3-methoxyphenol (0.124 g, 1.00 mmol) in THF (0.5 mL). The reaction mixture was stirred over night at room temperature, concentrated, and put through a silica column using toluene/EtOAc (7:3) as eluent. Solvents were removed *in vacuo* and the *N*-*t*-BOC derivative of the title compound was treated with CH_2Cl_2/TFA/H_2O (50:45:5; 5 mL) for 15 min. The mixture was concentrated and the residue was purified by silica chromatography using EtOAc/HOAc/MeOH/H_2O (20:3:3:2) as eluent. The product-containing fractions were concentrated, washed between CH_2Cl_2/5% aqueous NaOH, and put through a silica column using CH_2Cl_2/MeOH (8:2) as eluent to give 40 mg (34%) of the title compound as an oil. HRMS *m/z* calcd for $C_{17}H_{22}N_4O_3$ $(M)^+$ 330.1692, found 330.1677.

EXAMPLE 11

1-[2-(3-n-Butyloxyphenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.

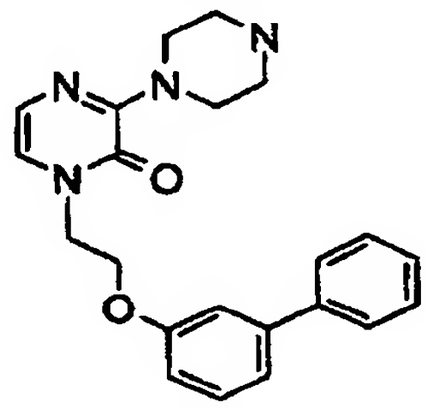


TMAD (0.060 g, 0.35 mmol) was dissolved in THF (1 mL) and DMF (0.5 mL) and the solution was added dropwise to a mixture of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.100 g, 0.310 mmol), triphenylphosphine (0.092 g, 0.35 mmol) and 3-*n*-butyloxyphenol (0.166 g, 1.00 mmol) in THF (0.5 mL). The

reaction mixture was stirred over night at room temperature, concentrated, and put through a silica column using toluene/EtOAc (7:3) as eluent. Solvents were removed in vacuo and the resulting *N*-*t*-BOC derivative was treated with CH_2Cl_2/TFA/H_2O (50:45:5; 5 mL) for 15 min with stirring. The mixture was concentrated and the residue purified by silica chromatography using EtOAc/HOAc/MeOH/H_2O (20:3:3:2) as eluent. The product-containing fractions were concentrated, washed between CH_2Cl_2/5% aqueous NaOH, and put through a silica column using CH_2Cl_2/MeOH (8:2) as eluent to give 97 mg (7%) of the title compound. HRMS *m/z* calcd for $C_{20}H_{28}N_4O_3$ $(M)^+$ 372.2161, found 372.2149.

EXAMPLE 12

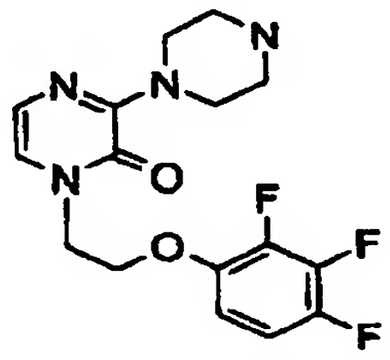
1-[2-([1,1'-Biphenyl]-3-yloxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



TMAD (0.060 g, 0.35 mmol) was dissolved in THF (1 mL) and DMF (0.5 mL) and the solution was added dropvise to a mixture of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.100 g, 0.31 mmol), triphenylphosphine (0.092 g, 0.35 mmol) and 3-phenylphenol (0.170 g, 1.00 mmol) in THF (0.5 mL). The reaction mixture was stirred over night at room temperature, concentrated, and put through a silica column using toluene/EtOAc (7:3) as eluent. Solvents were removed in vacuo and the resulting *N*-*t*-BOC derivative was treated with CH_2Cl_2/TFA/H_2O (50:45:5; 5 mL) for 15 min with stirring. The mixture was concentrated and the residue purified by silica chromatography using EtOAc/HOAc/MeOH/H_2O (20:3:3:2) as eluent. The product-containing fractions were concentrated, washed between CH_2Cl_2/5% aqueous NaOH, and put through a silica column using CH_2Cl_2/MeOH (8:2) as eluent to give 16 mg (16%) of the title compound. HRMS *m/z* calcd for $C_{22}H_{24}N_4O_2$ $(M)^+$ 376.1899, found 376.1888.

EXAMPLE 13

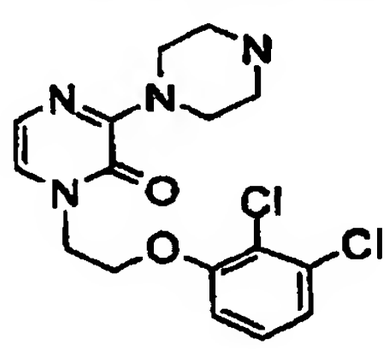
3-(1-Piperazinyl)-1-[2-(2,3,4-trifluorophenoxy)ethyl]-2(1H)-pyrazinone.



TMAD (0.207 g, 1.20 mmol) was added to a solution of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.324 g, 1.00 mmol), triphenylphosphine (0.315 g, 1.20 mmol) and 2,3,4-trifluorophenol (0.296 g, 2.0 mmol) in THF (1 mL) at room temperature. After being stirred for 2 h, the mixture was concentrated in vacuo and put through a silica column using toluene/EtOAc (7:3) as eluent. Solvents were removed in vacuo and the resulting *N*-*t*-BOC derivative was treated with CH_2Cl_2/TFA/H_2O (50:45:5; 5 mL) for 15 min with stirring. The mixture was concentrated and the residue purified by silica chromatography using EtOAc/HOAc/MeOH/H_2O (20:3:3:2) as eluent. The product-containing fractions were concentrated, washed between CH_2Cl_2/5% aqueous NaOH, and put through a silica column using CH_2Cl_2/MeOH (8:2) as eluent to give 62 mg (17%) of the title product. HRMS *m/z* calcd for $C_{16}H_{17}F_3N_4O_2$ $(M)^+$ 354.1304, found 354.1321.

EXAMPLE 14

1-[2-(2,3-Dichlorophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.

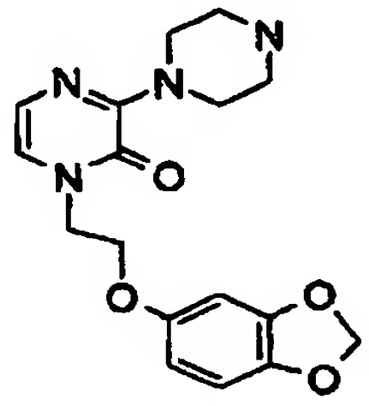


TMAD (0.207 g, 1.20 mmol) was added to a solution of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.324 g, 1.00 mmol), triphenylphosphine (0.315 g, 1.20 mmol) and 2,3-dichlorophenol (0.326 g, 2.0 mmol) in THF (1 mL) at room temperature. After being stirred for 2 h, the mixture was concentrated in vacuo and put through a silica column using toluene/EtOAc (7:3) as eluent. Solvents were removed in vacuo and the resulting *N*-*t*-BOC derivative was treated with CH_2Cl_2/TFA/H_2O (50:45:5; 5 mL) for 15 min with stirring. The mixture was

concentrated and the residue purified by silica chromatography using EtOAc/HOAc/MeOH/H_2O (20:3:3:2) as eluent. The product containing fractions were concentrated, washed between CH_2Cl_2/5% aqueous NaOH, and put through a silica column using CH_2Cl_2/MeOH (8:2) as eluent to give 60 mg, (16%) of the title compound. HRMS *m/z* calcd for $C_{16}H_{18}Cl_2N_4O_2$ $(M)^+$ 368.0807, found 368.0818.

EXAMPLE 15

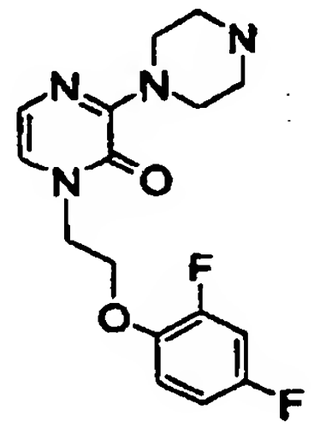
1-[2-(1,3-Benzodioxol-5-yloxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



TMAD (0.207 g, 1.20 mmol) was added to a solution of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.324 g, 1.00 mmol), triphenylphosphine (0.315 g, 1.20 mmol) and sesamol (0.173 g, 1.25 mmol) in THF (1 mL) at room temperature. After being stirred for 2 h, the reaction mixture was concentrated and put through a silica column using toluene/EtOAc (7:3) as eluent. Solvents were removed in vacuo and the resulting *N*-*t*-BOC derivative was treated with CH_2Cl_2/TFA/H_2O (50:45:5; 5 mL) for 15 min with stirring. The mixture was concentrated and the residue purified by silica chromatography using EtOAc/HOAc/MeOH/H_2O (20:3:3:2) as eluent. The product containing fractions were concentrated, washed between CH_2Cl_2/5% aqueous NaOH, and put through a silica column using CH_2Cl_2/MeOH (8:2) to give 78 mg (23%) of the title compound. HRMS *m/z* calcd for $C_{17}H_{20}N_4O_4$ $(M)^+$ 344.1485, found 344.1474.

EXAMPLE 16

1-[2-(2,4-Difluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



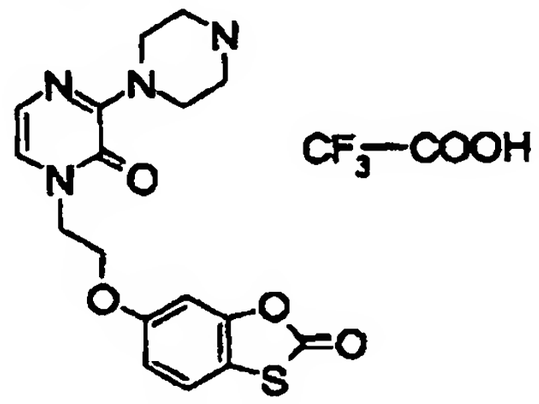
TMAD (0.129 g, 0.75 mmol) was added to a solution of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.200 g, 0.62 mmol), triphenylphosphine (0.196 g, 1.23 mmol) and 2,4-difluorophenol (0.160 g, 1.23 mmol) in THF (1 mL) at room temperature. After being stirred for 2 h, the mixture was concentrated and put through a silica column using toluene/EtOAc (7:3) as eluent. Solvents were removed in vacuo and the resulting *N*-*t*-BOC derivative was treated with CH_2Cl_2/TFA/H_2O (50:45:5; 5 mL) for 15 min with stirring. The mixture was concentrated and the residue purified by silica chromatography using EtOAc/HOAc/MeOH/H_2O (20:3:3:2) as eluent. The product-containing fractions were concentrated, washed between CH_2Cl_2/5% aqueous NaOH, and put through a silica column using CH_2Cl_2/MeOH (8:2) as eluent to give 30 mg (14%) of the title product. HRMS *m/z* calcd for $C_{16}H_{18}F_2N_4O_2$ $(M)^+$ 336.1398, found 336.1392.

EXAMPLES 17 AND 18. GENERAL PROCEDURE:

TMAD (0.207 g, 1.20 mmol) was added to a mixture containing 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (0.325 g, 1.00 mmol), triphenylphosphine (0.328 g, 1.25 mmol) and the appropriate phenol (1.25 mmol). The reaction mixture was stirred until the starting material was consumed (by HPLC: 2-6 h) then concentrated and purified by silica gel chromatography using toluene/EtOAc (9:1 to 1:1) eluent. The *N*-BOC derivative of the title compound was treated with CH_2Cl_2/TFA/H_2O (50:45:5; 5 mL) for 15 min with stirring. The mixture was concentrated and the residue purified by silica gel chromatography using a gradient of CH_2Cl_2 → CH_2Cl_2/MeOH (8:2) as eluent to provide the title compound.

EXAMPLE 17

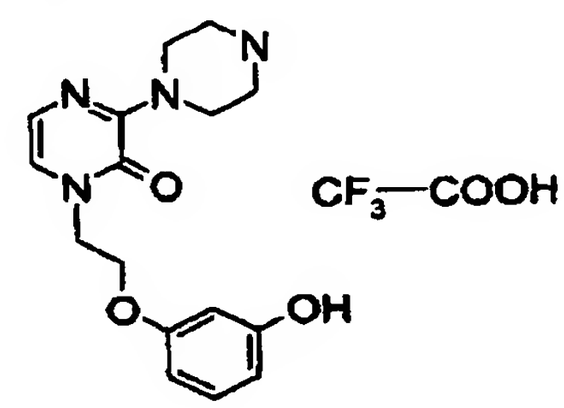
1-{2-[(2-Oxo-1,3-benzoxathiol-6-yl)oxy]ethyl}-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 6-hydroxy-1,3-benzoxathiol-2-one (0.210 g, 1.25 mmol). Yield: 0.147 g (30%). HRMS *m/z* calcd for $C_{17}H_{18}N_4O_4S$ $(M)^+$ 374.1049, found 374.1044. Anal ($C_{17}H_{18}N_4O_4S \cdot C_2F_3HO_2$) C, H, N.

EXAMPLE 18

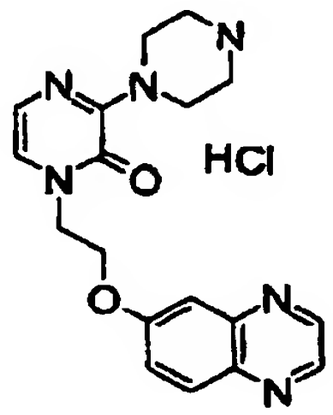
1-[2-(3-Hydroxyphenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from resorcinol (0.276 g, 0.25 mmol). Yield: 0.159 g (37%). HRMS *m/z* calcd for $C_{16}H_{20}N_4O_3$ $(M)^+$ 316.1535, found 316.1546.

EXAMPLE 19

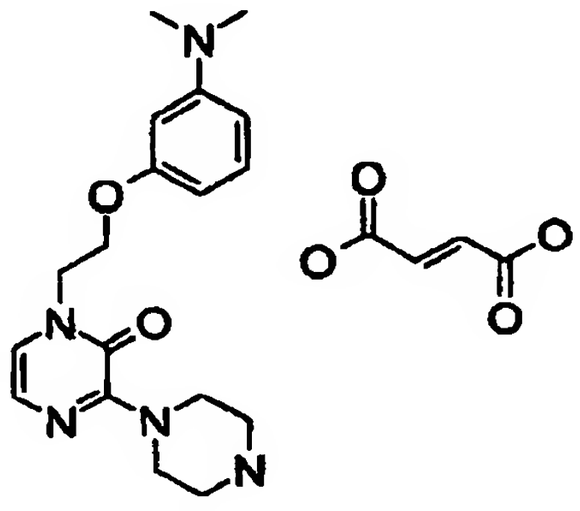
3-(1-Piperazinyl)-1-[2-(6-quinoxalinyloxy)ethyl]-2(1H)-pyrazinone, Hydrochloride.



TMAD (0.55 g, 3.20 mmol) was added to a stirred mixture of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (1.00 g, 3.08 mmol), 6-hydroxyquinoxaline* (0.45 g, 3.08 mmol) and triphenylphosphine (0.85 g, 3.24 mmol) in THF (10 mL) at room temperature. After 20 h, the reaction mixture was concentrated and put through a silica column using toluene/EtOAc (1:1) as eluent. The chromatographic procedure was repeated once. Solvents were removed in vacuo and the resulting *N*-*t*-BOC derivative was treated with CH_2Cl_2/TFA/H_2O (50:45:5; 20 mL) for 30 min with stirring. The reaction mixture was concentrated, dissolved in 0.1 M aqueous HCl and washed with toluene. The aqueous phase was frozen and lyophilized, dissolved in EtOH and concentrated to give 0.843 g (70%) of the title compound. HRMS *m/z* calcd for $C_{18}H_{20}N_6O_2$ $(M)^+$ 352.1648, found 352.1642. Anal ($C_{18}H_{20}N_6O_2 \cdot C_2HF_3O_2 \cdot 0.2\ H_2O$) C, H, N. *Prepared as described in J. Org. Chem. 1951, 16, 438-442.

EXAMPLE 20

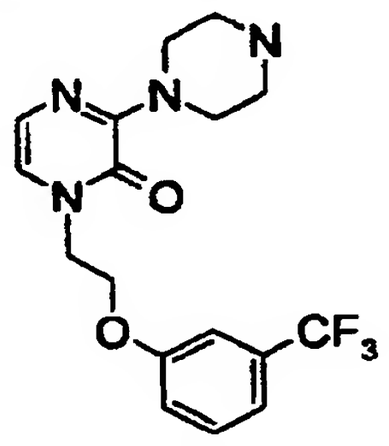
1-{2-[3-(N,N-Dimethylamino)phenoxy]ethyl}-3-(1-piperazinyl)-pyrazin-2(1H)-one, Fumarate.



3-Dimethylaminophenol (0.97 g, 3.70 mmol), triphenylphosphine (0.97 g, 3.70 mmol) and TMAD (0.64 g, 3.70 mmol) were added to a stirred solution of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (1.2 g, 3.70 mmol) in dry THF (10 mL) at room temperature. After 24 h, the reaction mixture was filtered and concentrated in vacuo. The residue was subjected to column chromatography on silica gel using toluene/EtOAc (3:1) containing 5% triethylamine as eluent to give 1.30 g (81%) of the *N*-*t*-BOC derivative of the title compound as an oil. This material (1.28 g, 2.89 mmol) was dissolved in CH_2Cl_2 (5 mL) and TFA (5 mL) was added. After being stirred at room temperature for 4 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and the solution was washed sequentially with aqueous 2 M NaOH, H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc/MeOH (3.5:0.5) containing 5% triethylamine as eluent to furnish 0.35 g of the free base of the title compound. This material (1.03 mmol) was dissolved in dry MeOH (3 mL) and fumaric acid (0.12 g, 1.03 mmol) in dry MeOH (3 mL) was added dropwise. Diethyl ether was added dropwise and the precipitate was filtered, washed with diethyl ether, dried, to give 0.37 g (22 %) of the title compound; mp. 180-191° C. Anal. ($C_{18}H_{25}N_5O_2 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 21

3-(1-Piperazinyl)-1-{2-[3-(trifluoromethyl)phenoxy]ethyl}-2(1H)-pyrazinone.



(TMAD; 129 mg, 0.75 mmol) was added to a mixture of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (200 mg, 0.62 mmol), triphenylphosphine (323 mg, 1.23 mmol), 3-hydroxybenzotrifluoride (199 mg, 1.23 mmol) in THF (1.5 mL). After being stirred for 1 h at room temperature, the reaction

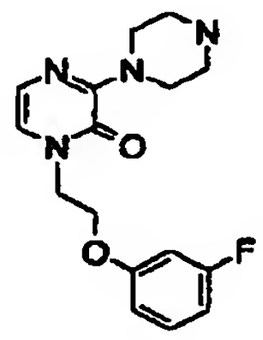
mixture was concentrated in vacuo and the residue was purified by chromatography on silica gel using toluene/EtOAc (7:3) as eluent. The combined fractions were concentrated and the resulting *N*-*t*-BOC derivative was treated with CH_2Cl_2/TFA/H_2O (50:45:5) for 30 min with stirring. The mixture was concentrated in a speed vac over night and the residue purified by chromatography on silica gel using $CHCl_3$/MeOH (9:1) as eluent to afford 109 mg (49%) of the title HRMS *m/z* calcd for $C_{17}H_{19}F_3N_4O_2$ $(M)^+$ 368.1460, found 368.1465.

EXAMPLES 22-24: GENERAL PROCEDURE:

TMAD (256 mg, 1.5 mmol) was added to a mixture of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (400 mg, 1.24 mmol), triphenylphosphine (646 mg, 2.46 mmol), and the appropriate phenol (1.23 mmol) in dry THF (3 mL) at room temperature. After being stirred for 4 h, the reaction mixture was concentrated in vacuo and the residue purified by chromatography on silica gel, using toluene/EtOAc (8:2) as eluent. Solvents were removed in vacuo and the resulting *N*-*t*-BOC derivative of the title compound was treated with CH_2Cl_2/TFA/H_2O (50:45:5) for 30 min. The mixture was concentrated in a speed vac over night. The residue was partitioned between 5 M aqueous NaOH/CH_2Cl_2 and the organic layer was dried over K_2CO_3. Removal of the solvent in vacuo and purification by chromatography on silica gel using $CHCl_3$/MeOH (9:1) as eluent gave the title compound.

EXAMPLE 22

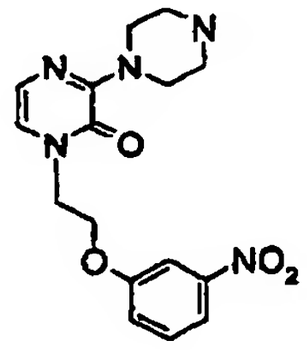
1-[2-(3-Fluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



The title compound was prepared according to the procedure described above starting from 3-fluorophenol. Yield: 228 mg (58%). HRMS *m/z* calcd for $C_{16}H_{19}FN_4O_2$ $(M)^+$ 318.1492, found 318.1487.

EXAMPLE 23

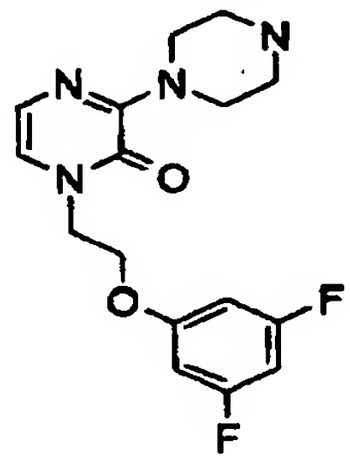
1-[2-(3-Nitrophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



The title compound was prepared according to the general procedure described above starting from 3-nitrophenol. Yield: 195 mg (46%); mp 171 °C. HRMS *m/z* calcd for $C_{16}H_{19}N_5O_4$ $(M)^+$ 345.1437, found 345.1420.

EXAMPLE 24

1-[2-(3,5-Difluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



The title compound was prepared according to the general procedure described above starting from 3,5-difluorophenol. Yield: 123 mg (20%); mp 119-121 °C. HRMS *m/z* calcd for $C_{16}H_{18}F_2N_4O_2$ $(M)^+$ 336.1398, found 336.1409.

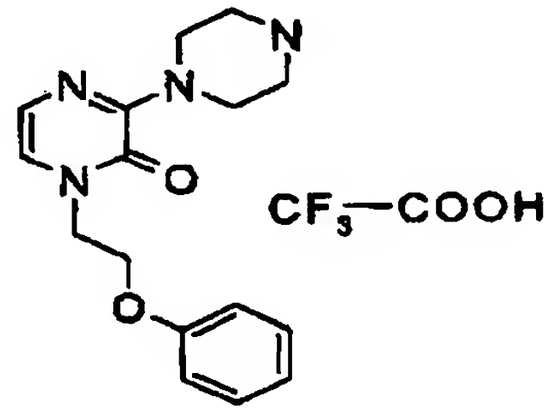
EXAMPLES 25-37: GENERAL PROCEDURE:

TMAD (103 mg, 0.60 mmol) was added to a mixture of 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-pyrazinyloxy]ethanol (97 mg, 0.30 mmol; Examples 25-34) or 2-[3-(4-*tert*-butoxycarbonyl-3-methyl-1-piperazinyl)-pyrazinyloxy]ethanol* (102 mg, 0.30 mmol; Examples 35-37), triphenylphosphine (157 mg, 0.60 mmol), and the appropriate phenol (0.60 mmol) in DMF (3.2 mL). The mixture was stirred under nitrogen at room temperature for approximately 18 h. The reaction mixture was filtered through a syringe with Celite and concentrated in a speed-vac. The *N*-*t*-BOC derivative of the title compound was dissolved in CH_3CN (1 mL) and purified by

preparative HPLC. The product-containing fractions were pooled and concentrated in a speed-vac. *N*-Deprotection: The *N*-*t*-BOC intermediate was dissolved in CH_2Cl_2 (2 mL) and TFA (1 mL) was added at 0 °C. The temperature was allowed to rise to room temperature and the mixture was stirred for 1 h. The reaction mixture was concentrated in a speed-vac to furnish the title compound. *Prepared as described in Example 44.

EXAMPLE 25

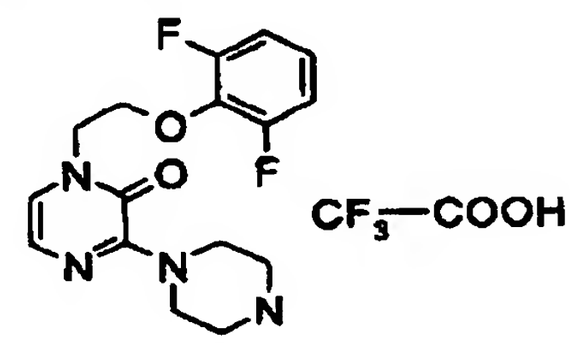
1-[2-(Phenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from phenol (56 mg, 0.60 mmol). Yield: 22 mg (18%). HPLC purity: 100%. MS *m/z* 301 $(M+H)^+$.

EXAMPLE 26

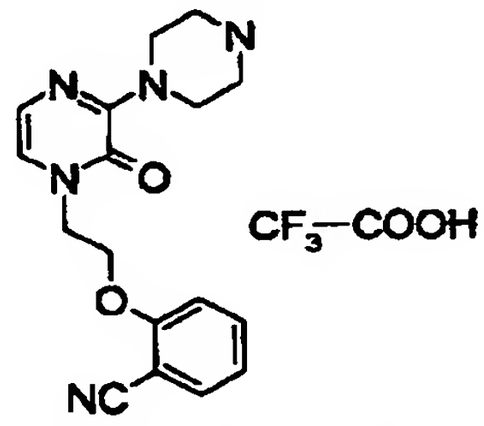
1-[2-(2,6-Difluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 2,6-difluorophenol (78 mg, 0.60 mmol). Yield: 55 mg (41%). HPLC purity: 99%. MS *m/z* 337 $(M+H)^+$.

EXAMPLE 27

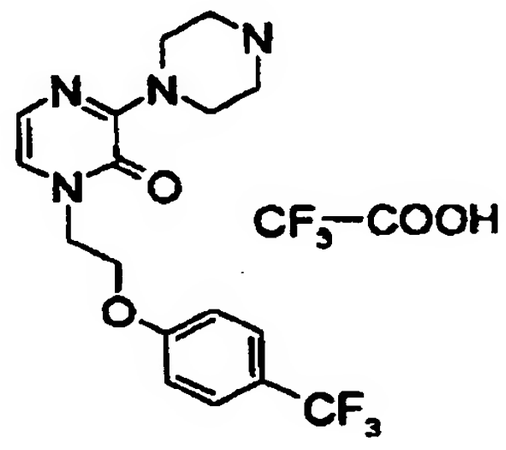
1-[2-(2-Cyanophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazin ne, Triflu roacetate.



The title compound was prepared according to the procedure described above starting from 2-cyanophenol (71 mg, 0.60 mmol). Yield: 47 mg (36%). HPLC purity: 96%. MS *m/z* 326 $(M+H)^+$.

EXAMPLE 28

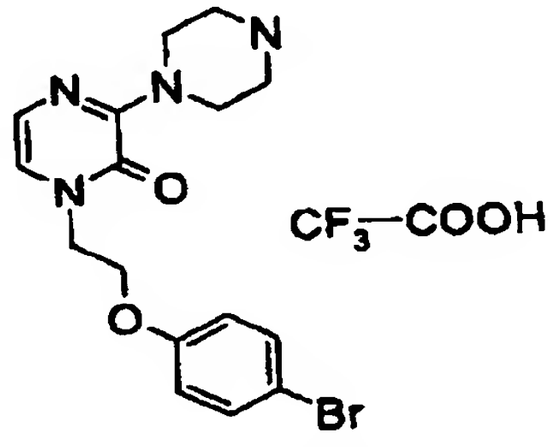
1-[2-(4-Trifluoromethylphenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 4-trifluoromethylphenol (97 mg, 0.60 mmol). Yield: 20 mg (14%). HPLC purity: 100%. MS *m/z* 369 $(M+H)^+$.

EXAMPLE 29

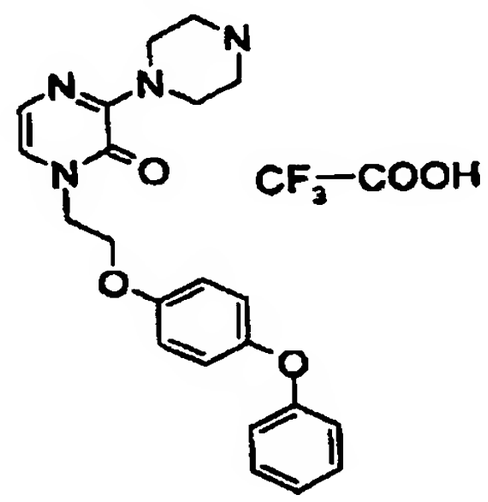
1-[2-(4-Bromophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 4-bromophenol (104 mg, 0.60 mmol). Yield: 29 mg (20%). HPLC purity: 99%. MS *m/z* 380 $(M+H)^+$.

EXAMPLE 30

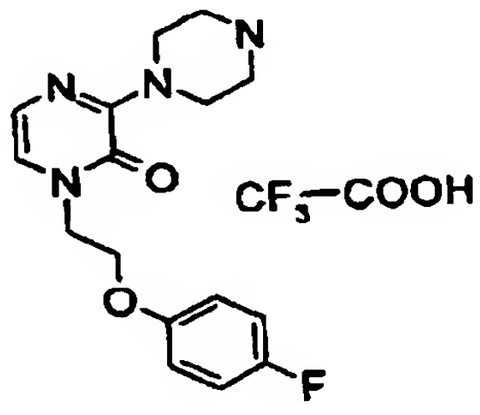
1-[2-{4-Phenoxy-(phenoxy)}ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 4-phenoxyphenol (112 mg, 0.60 mmol). Yield: 20 mg (13%). HPLC purity: 96%. MS *m/z* 393 $(M+H)^+$.

EXAMPLE 31

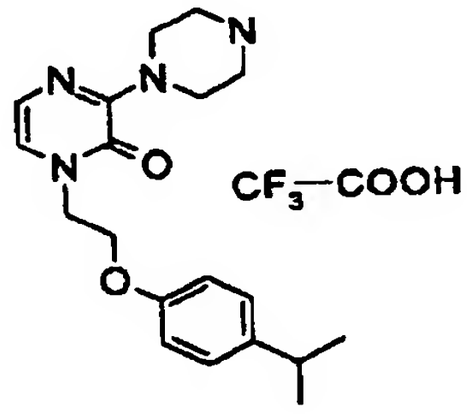
1-[2-(4-Fluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 4-fluorophenol (67 mg, 0.60 mmol). Yield: 36 mg (28%). HPLC purity: 100%. MS *m/z* 319 $(M+H)^+$.

EXAMPLE 32

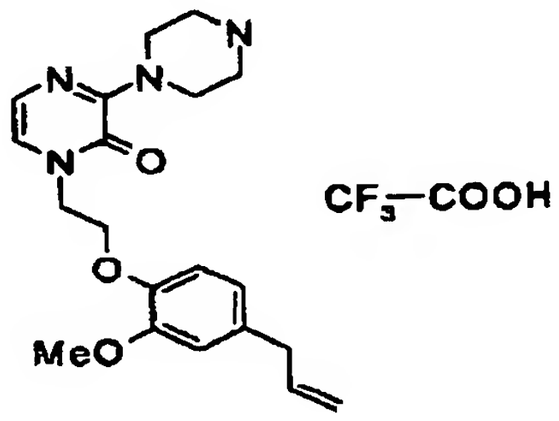
1-[2-(4-Isopropylphenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 4-isopropylphenol (82 mg, 0.60 mmol). Yield: 59 mg (43%). HPLC purity: 99%. MS *m/z* 343 $(M+H)^+$.

EXAMPLE 33

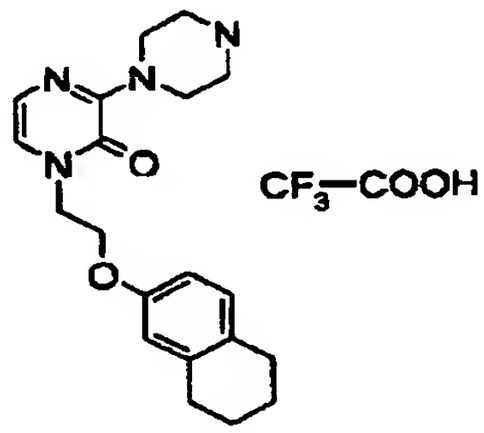
1-[2-{(4-Allyl-2-methoxy)phenoxy}ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 4-allyl-2-methoxyphenol (99 mg, 0.60 mmol). Yield: 69 mg (47%). HPLC purity: 98%. MS *m/z* 371 $(M+H)^+$.

EXAMPLE 34

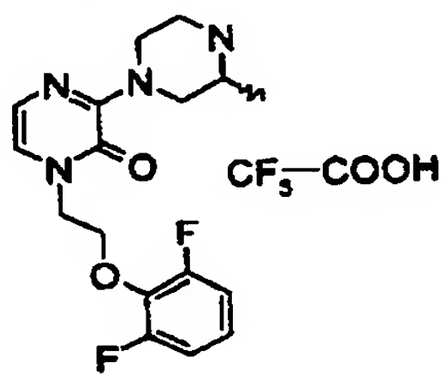
1-[2-(5,6,7,8-Tetrahydro-naphthalen-2-yloxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 5,6,7,8-tetrahydro-naphthalen-2-ol (89 mg, 0.60 mmol). Yield: 26 mg (19%). MS *m/z* 355 $(M+H)^+$.

EXAMPLE 35

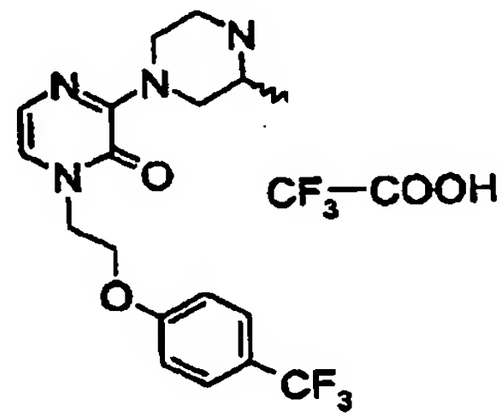
1-[2-(2,6-Difluorophenoxy)ethyl]-3-(3-methyl-1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 2,6-difluorophenol (78 mg, 0.60 mmol). Yield: 71 mg (51%). HPLC purity: 99%. MS *m/z* 351 $(M+H)^+$.

EXAMPLE 36

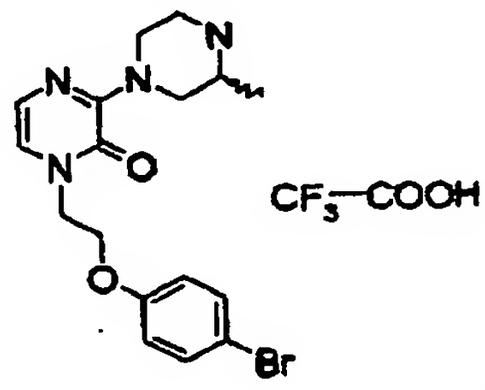
1-[2-(4-Trifluoromethylphenoxy)ethyl]-3-(3-methyl-1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 4-trifluoromethylphenol (97 mg, 0.60 mmol). Yield: 82 mg (55%). HPLC purity: 99%. MS *m/z* 383 $(M+H)^+$.

EXAMPLE 37

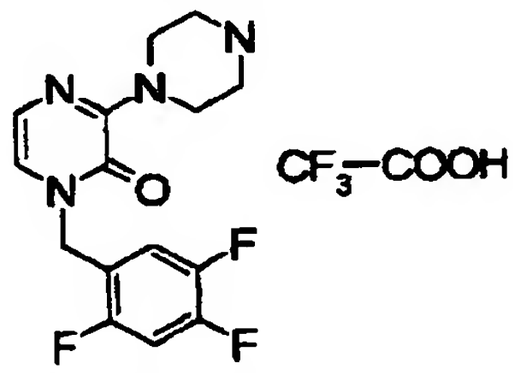
1-[2-(4-Bromophenoxy)ethyl]-3-(3-methyl-1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



The title compound was prepared according to the procedure described above starting from 4-bromophenol (104 mg, 0.60 mmol). Yield: 79 mg (52%). HPLC purity: 98%. MS *m/z*394 $(M+H)^+$.

EXAMPLE 38

1-(2,4,5-Trifluorobenzyl)-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



Step 1: 3-(4-tert-Butoxycarbonyl-1-piperazinyl)-2(1H)-pyrazinone.

2-Chloro-3-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrazine* (60 g, 0.20 mol) was added to a mixture of NaOH (100 g, 2.5 mol), water (100 mL) and DMSO (100 g) at 100 °C. After being stirred for 3 h, the mixture was allowed to cool and partitioned between toluene (100 g) and water (200 mL). Water (300 mL), crushed ice (200 g), EtOAc (600 g) and sodium chloride (100 g) were added to the aqueous layer. The layers were separated and the aqueous layer was extracted with an additional portion of EtOAc (600 g). The combined organic layers were concentrated in vacuo to furnish 38 g (68%) of the title product. ^{1}NMR data supports the stated structure.

*Prepared according to the procedure described in WO 00/76984.

Step 2. 1-(2,4,5-Trifluorobenzyl)-3-(4-tert-Butoxycarbonyl-1-piperazinyl)-2(1H)-pyrazinone.

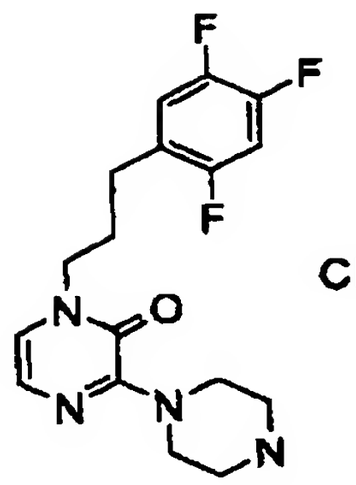
To a solution of 3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-2(1*H*)-pyrazinone (obtained in Step 1 above; 1.30 g, 4.66 mmol) in THF (20 mL) was added *t*-BuOK (0.53 g, 4.66 mmol) and the mixture was stirred at room temperature for 10 min. The resulting solution was added dropwise to a stirred solution of 2,4,5-trifluorobenzyl bromide (1.20 g, 5.33 mmol) in THF (20 mL) at room temperature. After 2 h, the reaction mixture was cooled to 0 °C and partitioned between water (20 mL) and EtOAc (50 mL). The organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent gave 1.82 g (96%) of the title compound as an oil which crystallized upon standing. The product can be recrystallized from *tert*-butyl methyl ether. HPLC purity: 94%. ^{1}NMR and MS analyses support the stated structure.

Step 3. 1-(2,4,5-Trifluorobenzyl)-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.

To a solution of 1-(2,4,5-trifluorobenzyl)-3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-2(1*H*)-pyrazinone (obtained in Step 2 above; 0.50 g, 1.18 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL) dropwise at 0 °C. After being stirred for 1 h at room temperature, the solvent and TFA were removed in vacuum resulting in a colorless oil. Trituration with ether gave white crystals which were filtered off after cooling the mixture to 0 °C. The crystals were washed with cold ether and dried in vacuum at 50 °C to furnish 0.50 g (98%) of the title compound. HPLC purity: 95%. ^{1}H NMR supports the stated structure. HRMS *m/z* calcd for $C_{15}H_{15}F_3N_4O$ $(M)^+$ 324.1198, found 324.1195.

EXAMPLE 39

1-[3-(2,4,5-Trifluorophenyl)propyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.



$CF_3—COOH$

Step 1. 3-(2,4,5-Trifluorophenyl)propionic acid.

3-(2,4,5-Trifluorophenyl)acrylic acid (3.50 g, 17.3 mmol) was dissolved in glacial acetic acid (40 mL) and treated with active carbon (~0.5 g). The mixture was stirred for 20 min, the carbon filtered off and washed with glacial acetic acid (20 mL). To the resulting solution Pd on carbon catalyst (0.45 g, 10% Pd) was added and the mixture was stirred under hydrogen at atmospheric pressure overnight. The suspension was filtered and concentrated in vacuo. Residual acetic acid was removed by addition of a small volume of toluene followed by concentration in vacuo. The resulting oil crystallized upon standing and this material was dried in vacuum at 50 °C to give 3.34 g (95%) of the title compound.

Step 2. 3-(2,4,5-Trifluorophenyl)propan-1-ol.*

3-(2,4,5-Trifluorophenyl)propionic acid (obtained in Step 1 above; 3.25 g, 16.0 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. To this solution was added $Me_2S·BH_3$ (3.2 mL, ~32 mmol) dropwise under 30 min and the resulting mixture was then heated at 70 °C for 30 min. After cooling to 0 °C, 6 M aqueous HCl (20 mL) was added dropwise. The mixture was heated at 70 °C for 1 hour. After cooling to room temperature the mixture was extracted with ether (2x20 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation and drying in vacuum gave the title compound as a colorless liquid (3.17 g, 97% pure by HPLC) that was used directly in the next step. *Previously reported in EP 369812.

Step 3. 3-(2,4,5-Trifluorophenyl)propyl Methanesulfonate.

Methanesulfonyl chloride (0.45 g, 3.88 mmol) was added dropwise to a solution of 3-(2,4,5-trifluorophenyl)propan-1-ol (obtained in Step 2 above; 0.46 g, 2.41 mmol) and triethylamine (0.71 g, 7.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was

stirred at room temperature for 2 h. After complete disappearance of the alcohol (HPLC monitoring), CH_2Cl_2 (10 mL) and water (10 mL) were added. The aqueous phase was saturated with NaCl and extraction performed. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give 0.66 g (100%) of the title compound as a yellow oil. Purity by HPLC: 87%. This material was used directly in the next step.

Step 4: 1-[3-(2,4,5-Trifluorophenyl)propyl]-3-(4-tert-butoxycarbonyl-1-piperazinyl)-2(1H)-pyrazinone.

To a solution of 3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-2(1*H*)-pyrazinone (obtained in Example 38, Step 1; 0.53 g, 1.91 mmol) in THF (10 mL) was added *t*-BuOK (0.21 g, 1.91 mmol) and the mixture was stirred at room temperature for 10 min. The resulting solution was added dropwise to 3-(2,4,5-trifluorophenyl)propyl methanesulfonate (0.66 g, ~2.1 mmol) dissolved THF (10 mL). The mixture was stirred at 35 °C for 3 days. Then, the solution was cooled to 0 °C and water (20 mL) and EtOAc (25 mL) were added. The aquous phase was saturated with NaCl (2 g) and extraction performed. After separation and repeated extraction with EtOAc (15 mL) the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuum gave 0.75 g of a yellowish oil which was purified by column chromatography on silica gel using EtOAc/*n*-hexane (4:1) as eluent. This gave 0.50 g (57%) of the title compound as a colorless oil. HPLC purity: 91%. ^1H NMR and MS analyses supported the stated structure.

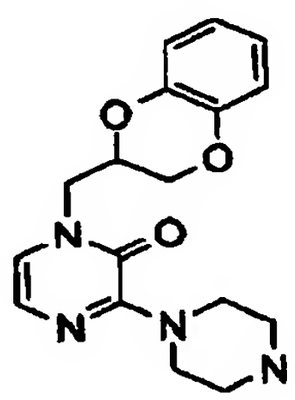
Step 5. 1-[3-(2,4,5-Trifluorophenyl)propyl]-3-(1-piperazinyl)-2(1H)-pyrazinone, Trifluoroacetate.

TFA (2 mL) was added dropwise to a solution of 1-[3-(2,4,5-trifluorophenyl)propyl]-3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-2(1*H*)-pyrazinone (obtained in Step 4 above; 0.46 g, 1.02 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred for 1 hour at room temperature, the solvent and TFA were removed in vacuum resulting in a colorless oil. Trituration with ether gave pale white crystals which were filtered off after cooling the mixture to 0 °C. The crystals were washed with cold ether and dried in vacuum at 50 °C to furnish 0.38 g (79%) of the title compound. HPLC purity: 96%.

^{1}H NMR supports the stated structure. HRMS *m/z* calcd for $C_{17}H_{19}F_3N_4O$ $(M)^+$ 352.1511, found 352.1524.

EXAMPLE 40

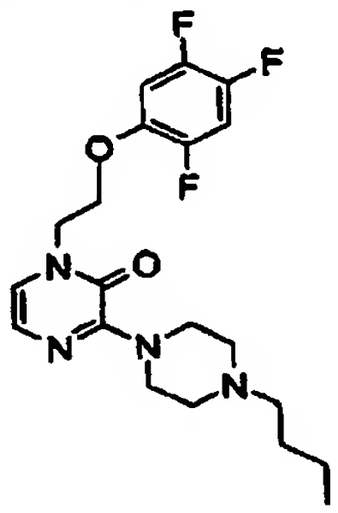
1-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-3-(1-piperazinyl)-2(1H)-pyrazinone.



The title compound was prepared according to the procedure described in Example 39, Step 4 and 5, starting from 3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-2(1*H*)-pyrazinone (obtained in Example 38, Step 1) and 2-chloromethyl-2,3-dihydro-benzo[1,4]dioxine. HPLC purity: 97%. MS and NMR analyses support the stated structure. HRMS *m/z* calcd for $C_{17}H_{20}N_4O_3$ $(M)^+$ 328.1535, found 328.1538.

EXAMPLE 41

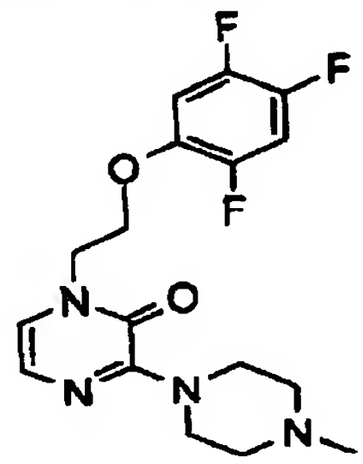
1-[2-(2,4,5-Trifluorophenoxy)ethyl]-3-(4-n-butyl-1-piperazinyl)-2(1H)-pyrazinone.



HRMS *m/z* calcd for $C_{20}H_{25}F_3N_4O_2$ $(M)^+$ 410.1930, found 410.1920.

EXAMPLE 42

1-[2-(2,4,5-Trifluorophenoxy)ethyl]-3-(4-methyl-1-piperazinyl)-2(1H)-pyrazinone.



Step 1. 1-(3-Chloro-2-pyrazinyl)-4-methylpiperazine.*

A mixture 2,3-dichloropyrazine (5.0 g, 34 mmol), *N*-methylpiperazine (5.1 g, 51 mmol) and potassium carbonate (7.0 g, 51 mmol) in acetonitrile (100 mL) was stirred at ambient temperature for 2 h. Addition of hexane, followed by filtration and concentration of the filtrate gave 7.3 g of a crude product as an orange liquid. Purification by filtration through silica using heptane/EtOAc (3:1) followed by EtOAc/acetone (1:1) gave 4.1 g (57%) of the title compound as a yellow oil which solidified upon cooling. HPLC purity: 100%. MS-EI *m/z* 241 $(M+H)^+$. *Reported in WO 00/76984.

Step 2. 3-(4-Methyl-1-piperazinyl)-2(1H)-pyrazinone.

To a solution of NaOH (5.4 g, 125 mmol) in a mixture of water/DMSO (1:1; 15 mL) at 80 °C was added 1-(3-chloro-2-pyrazinyl)-4-methylpiperazine (obtained in Step 1 above; 2.5 g, 12 mmol). After being stirred for 2 h, the dark red solution was cooled, extracted with EtOAc overnight to give, after drying and concentration of the solvent, 0.96 g (43%) of the title compound as an off-white solid. HPLC purity: 88%. MS-EI *m/z* 195 $(M+H)^+$.

Step 3. 2-(2,4,5-Trifluorophenoxy)ethanol.

Potassium *tert*-butoxide (3.0 g, 27 mmol) was added to a mixture of 1,2,4,5-tetrafluorobenzene (2.0g, 13.3 mmol) and ethylene glycol (7.5 mL, 133 mmol) in DMSO and heated at 80 °C for 1 h and then at 60 °C overnight. The title alcohol, as a white semisolid (1.5 g containing 14% EtOAc), was obtained by washing several times an EtOAc solution with water, dried and concentrated carefully under vacuum

at 30 °C. NMR analysis supported the stated structure. This material was used directly in the next step.

Step 4. 2-(2,4,5-Trifluorophenoxy)ethyl Methanesulfonate.

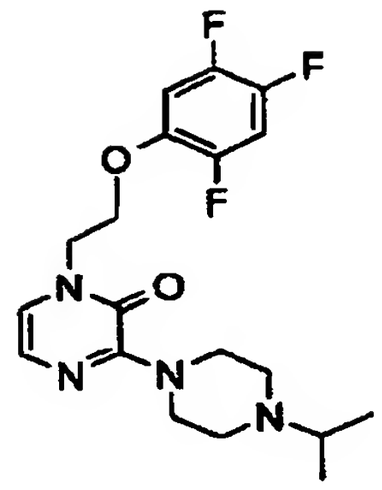
Triethylamine (1.8 mL, 13.2 mmol) was added to a cold solution of a mixture of the 2-(2,4,5-trifluorophenoxy)ethanol (1.3 g, 6.6 mmol) and methanesulfonyl chloride (0.61 mL, 7.9 mmol) in CH_2Cl_2 (40 mL). After 1.5 h, water was added and the mixture was concentrated. The residue was dissolved in EtOAc and the solution was washed with 1 M $KHSO_4$, then with brine, dried and concentrated to give 1.78 g of the title compound as an orange oil. NMR analysis supported the stated structure. This material was used directly in the next step.

Step 5. 1-[2-(2,4,5-Trifluorophenoxy)ethyl]-3-(4-methyl-1-piperazinyl)-2(1H)-pyrazinone.

A mixture of 3-(4-methyl-1-piperazinyl)-2(1*H*)-pyrazinone (obtained in Step 2 above; 0.5 g, 2.6 mmol) and *t*-BuOK (440 mg, 3.9 mmol) was stirred in THF (40 mL) until the mixture became thick (about 10 min), and then a solution of 2-(2,4,5-trifluorophenoxy)ethyl methanesulfonate (obtained in Step 4 above; 0.90 g, 2.2 mmol) in THF (10 mL) was added. After 5 days at ambient temp, HPLC showed only 50% conversion. The reaction solution was then heated to 60 °C overnight which gave almost full conversion. The reaction was worked up according to the following: water was added, THF was evaporated off and the aqueous mixture was extracted twice with EtOAc, dried and concentrated to yield 1.08 g of the crude product as a yellow oil. Purification using flash chromatography [eluent: 2% MeOH in $CHCl_3 + NH_3$ (g)] gave the title compound as a yellow oil, which solidified upon cooling. Yield 304 mg (32%). HPLC purity: 100%. MS-EI *m/z* 369 $(M+H)^+$. HRMS *m/z* calcd for $C_{17}H_{19}F_3N_4O_2$ $(M)^+$ 368.1460, found 368.1462.

EXAMPLE 43

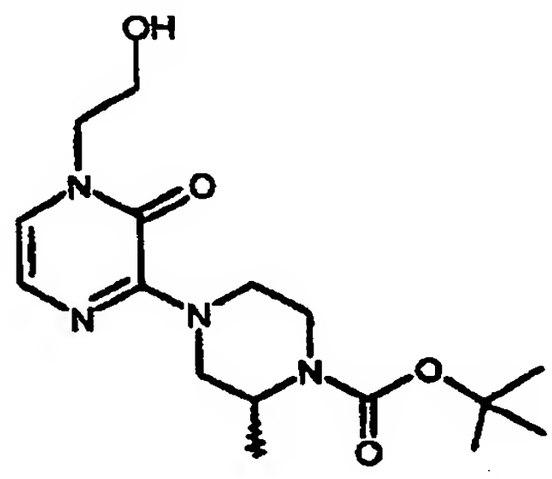
1-[2-(2,4,5-Trifluorophenoxy)ethyl]-3-(4-isopropyl-1-piperazinyl)-2(1H)-pyrazinone.



The title compound was prepared according to the procedure described in Example 42 starting from *N*-isopropylpiperazine. HPLC purity: 99%. MS-EI *m/z* 397 $(M+H)^+$. HRMS *m/z* calcd for $C_{19}H_{23}F_3N_4O_2$ $(M)^+$ 396.1773, found 396.1771.

EXAMPLE 44 (INTERMEDIATE)

2-[3-(4-tert-Butoxycarbonyl-3-methyl-1-piperazinyl)-pyrazinyloxy]ethanol.



Step 1. 2-Chloro-3-(3-methylpiperazin-1-yl)pyrazine.

A mixture of 2,3-dichloropyrazine (2.80 g, 18.8 mmol), racemic 2-methylpiperazine (1.88 g, 18.8 mmol) and K_2CO_3 (3.9 g, 28.2 mmol) in CH_3CN (25 mL) was heated at 65 °C for 15 h with stirring. The reaction mixture was filtered and concentrated. The crude product was purified by flash chromatography on silica gel using $CHCl_3$/MeOH (15:1) as eluent to give 3.2 g (79%) of the title compound. MS *m/z* 213 $(M+H)^+$.

Step 2. tert-Butyl 4-(3-chloropyrazin-2-yl)-2-methylpiperazine-1-carboxylate.

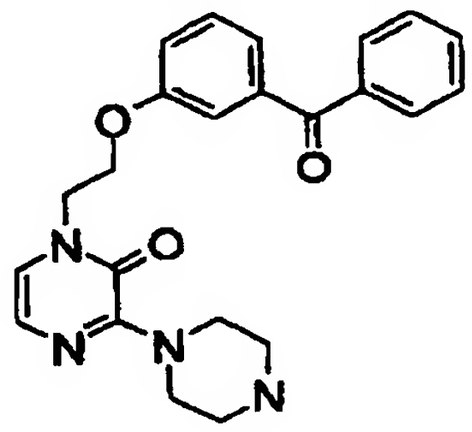
Triethylamine (1.82 g, 17.9 mmol) was added to a solution of 2-chloro-3-(3-methylpiperazin-1-yl)pyrazine (obtained in Step 1 above; 3.18 g, 15.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. *t*-BOC-anhydride (3.92 g, 17.9 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the resulting mixture was stirred at 0 °C for 30 min. The

mixture was allowed to warm to room temperature and stirring was continued for a further 15 h. The reaction mixture was washed with water, the organic layer dried over $MgSO_4$, and concentrated in vacuo to give 3.12 g (67%) of the title compound. MS *m/z* 313 $(M+H)^+$.

Step 3. 2-[3-(4-tert-Butoxycarbonyl-3-methyl-1-piperazinyl)-pyrazinyloxy]- ethanol. To a mixture of *tert*-butyl 4-(3-chloropyrazin-2-yl)-2-methylpiperazine-1-carboxylate (obtained in Step 2 above; 3.0 g, 9.6 mmol) in ethylene glycol (10 mL) and dioxane (30 mL) was added *t*-BuOK (1.18 g, 10.6 mmol). The resulting mixture was stirred at 90 °C, under N_2, overnight. Water (10 mL) was added to the light brown reaction mixture and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography using toluene/EtOAc (2:3) as eluent to furnish 3.19 g (98%) of the title compound. HPLC purity: 99%. MS *m/z* 339 $(M+H)^+$.

EXAMPLE 45

1-[2-(3-Benzoylphenoxy)ethyl]-3-(1-piperazinyl)-2(1H)-pyrazinone.



The title compound was prepared according to the general procedure described for Examples 22-24 starting from 3-benzoylphenol. Yield: 120 mg (24%); mp 69-70 °C. HRMS *m/z* calcd for $C_{23}H_{24}N_4O_3$ $(M)^+$ 404.1848, found 404.1835.

PREPARATION OF PHARMACEUTICAL COMPOSITIONS

EXAMPLE: Preparation of tablets

	Ingredients	mg/tablet
1.	Active compound	10.0
2.	Cellulose, microcrystalline	57.0
3.	Calcium hydrogen phosphate	15.0
4.	Sodium starch glycolate	5.0
5.	Silicon dioxide, colloidal	0.25
6.	Magnesium stearate	0.75

The active ingredient 1 is mixed with ingredients 2, 3, 4 and 5 for about 10 minutes. The magnesium stearate is then added, and the resultant mixture is mixed for about 5 minutes and compressed into tablet form with or without film-coating.

Pharmacological methods

The ability of a compound of the invention to bind or act at specific 5-HT receptor subtypes can be determined using *in vitro* and *in vivo* assays known in the art. The biological activity of compounds prepared in the Examples was tested using different tests.

Affinity assay

The 5-HT_{2A} receptor affinity of compounds in the Examples was determined in competition experiments, where the ability of each compound in serial dilution to displace ^{3}H-labeled lysergic diethyl amide (LSD), bound to membranes prepared from a transfected CHO cell line stably expressing the human 5-HT_{2A} receptor protein, was measured after rapid filtration through glass fiber filters. Non-specific binding was defined using mianserin (5 μM). The 5-HT_{2A} receptor affinity values are expressed as K_i values. Results obtained for exemplary compounds of the invention are illustrated in Table 1 below. The K_i values for the compounds towards the human 5-HT_{2A} receptor were in the range 0.5-1000 nM.

Table 1. Human 5-HT_{2A} receptor Affinity

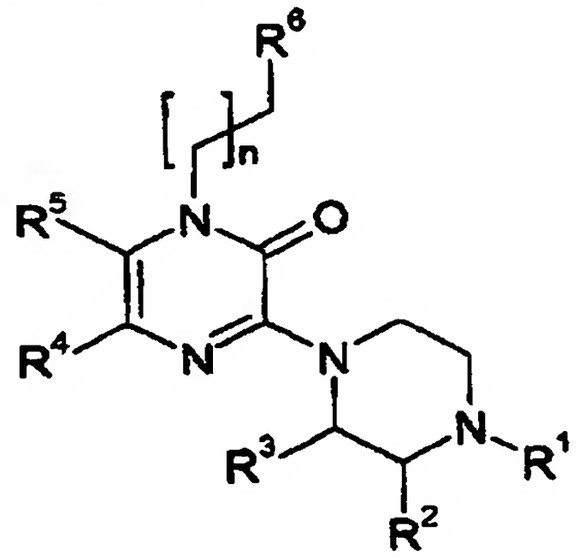
Compound	K_i (nM)
Example 13	29 nM
Example 29	8 nM

In vitro functional assay

The antagonist activity at the 5-HT_{2A} receptor of the compounds in the Examples of the present invention was judged from their inability to mobilise intracellular calcium in transfected CHO cells, stably expressing the human 5-HT_{2A} receptor protein, using the calcium-chelating fluorescent dye FLUO-3 (Sigma, St. Louis, MO, U.S.A.) at a substrate concentration of 1 μM. Additionally, the antagonist activity at the 5-HT_{2A} receptor of the said compounds could be verified by their ability to inhibit 5-HT-induced calcium release in transfected CHO cells, stably expressing the human 5-HT_{2A} receptor protein; using cumulative dose-response techniques. From these experiments, the apparent functional inhibitory constant K_b could be estimated.

CLAIMS

1. A compound of the general formula (I):



(I)

wherein

n is 0, 1, 2, 3 or 4;

R^1 is H, C_{1-6}-alkyl, aryl-C_1-C_3-alkyl, heteroaryl-C_1-C_3-alkyl, 2-hydroxyethyl, methoxy-C_2-C_4-alkyl, or C_1-C_4-alkoxycarbonyl; wherein

any aryl or heteroaryl residue may be substuted with C1-4-alkyl, C1-4-alkoxy, C1-4-alkylthio, halogen, trifluoromethyl, trifluoromethoxy or cyano;

R^2 and R^3 each, independently, represent H or CH_3;

R^4 and R^5 each, independently, represent H, halogen, methyl, or together with the ring, to which carbon atoms they are attached, form a 1*H*-quinoxalin-2-one nucleus; and

R^6 represents aryloxy, heteroaryloxy, arylthio, heteroarylthio, aryl-NH, heteroaryl-NH, aryl, or heteroaryl; wherein

any aryl or heteroaryl residue, alone or as part of another group, may be unsubstituted or substituted with one, two, three, four or five substituents, independently selected from aryl, aryl-C_{1-2}-alkyl, arylcarbonyl, heteroaryl, heteroaryl-C_{1-2}-alkyl, heteroarylcarbonyl, aryloxy, heteroaryloxy, arylthio, heteroarylthio, arylamino, heteroarylamino, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyloxy, C_{3-6}-cycloalkylcarbonyl, C_{1-6}-alkyl, C_{2-6}-alkanoyl, C_{2-6}-alkynyl, C_{2-6}-

alkenyl, or fluoro-C_{2-4}-alkyloxy, halogen, trifluoromethyl, nitro, cyano, trifluoromethoxy, trifluoromethylthi , C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino, C_{1-6}-dialkylamino, hydroxy or oxo;

wherein

any aryl or heteroaryl residue as substituents on aryl or heteroaryl, alone or as part of another group, in turn may be substituted in one or more positions, independently of each other, by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy or cyano;

and pharmaceutically acceptable salts , hydrates, geometrical isomers, tautomers, optical isomers, *N*-oxides and prodrug forms thereof, with the provisos that:

R^2 and R^3 are not both CH_3;

when R^1, R^2, R^4 and R^5 are H and R^3 is H or CH_3, then R^6 is not 3-pyridyloxy, 6-methyl-2-nitro-3-pyridyloxy, or 2-chloro-3-pyridyloxy;

when n = 0, then R^6 is not aryloxy, heteroaryloxy, arylthio, heteroarylthio, aryl-NH or heteroaryl-NH; and

the compound of formula (I) is not 1-benzyl-3-(4-methyl-piperazin-1-yl)-1*H*-quinoxalin-2-one.

2. The compound according to claim 1, wherein
any aryl or heteroaryl residue, alone or as part of another group, is substituted with one or two non-halogen substituents.

3. The compound according to claim 1, wherein
any aryl or heteroaryl residue, alone or as part of another group, is substituted with at least one halogen substituents.

4. The compound according to claim 1 or 2, wherein any aryl or heteroaryl residue that is a substituent on another aryl or heteroaryl, alone or as part of another group, in turn is substituted in one position.

5. The compound according to claim 1, wherein

$n = 1$;

R^1, R^2, R^3, R^4 and R^5 each are H; and

R^6 is phenoxy, where the phenyl ring of the said phenoxy group may be unsubstituted or substituted with one, two, three, four or five substituents.

6. The compound according to claim 5, wherein the phenyl ring of R^6 is substituted with one, two, three, four or five substituents independently selected from

halogen,
2-propenyl,
C_1-C_6-alkyl,
C_1-C_6-alkoxy,
trifluoromethyl,
phenyl,
phenoxy,
benzoyl, and
C_{3-6}-cycloalkyl;

wherein the phenyl, phenoxy or benzoyl substituent in turn may be substituted in one or more positions, independently of each other, by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy or cyano.

7. The compound according to claim 6, wherein the phenyl ring of R^6 is substituted with one or two non-halogen substituents.

8. The compound according to claim 6, wherein the halogen substituent is fluorine.

9. The compound according to claim 1, wherein

$n = 1$;

R^1 is C_1-C_6-alkyl;

R^2, R^3, R^4 and R^5 each are H; and

R^6 is 2,4,5-trifluorophenoxy.

10. The compound according to claim 1, wherein

n = 1;

R^1, R^2, R^3, R^4 and R^5 each are H; and

R^6 is 2-oxo-1,3-benzoxathiol-6-yloxy.

11. The compound according to claim 1 wherein

n = 0;

R^1, R^2, R^3, R^4 and R^5 each are H; and

R^6 is phenyl, where the said phenyl may be substituted with halogen, in one, two, three, four or five positions.

12. The compound according to claim 11 wherein the halogen is fluorine,

13. The compound according to anyone of claims 1 to 11, which is selected from the group consisting of:

- 1-[2-(2-fluoro-4-nitrophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-{2-[(2-oxo-2*H*-chromen-7-yl)oxy]ethyl}-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 3-(1-piperazinyl)-1-[2-(2,4,5-trifluorophenoxy)ethyl]-2(1*H*)-pyrazinone,
- 3-(1-piperazinyl)-1-[2-(2,3,5,6-tetrafluorophenoxy)ethyl]-2(1*H*)-pyrazinone,
- 1-[2-(2,3,4,5,6-pentafluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-chloro-2-fluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-cyanophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-cyclopentylphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(1,2-benzisoxazol-3-yloxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-methoxyphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-*n*-butyloxyphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,

- 1-[2-([1,1'-biphenyl]-3-yloxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 3-(1-piperazinyl)-1-[2-(2,3,4-trifluorophenoxy)ethyl]-2(1*H*)-pyrazinone,
- 1-[2-(2,3-dichlorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(1,3-benzodioxol-5-yloxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,4-difluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-{2-[(2-oxo-1,3-benzoxathiol-6-yl)oxy]ethyl}-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-hydroxyphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 3-(1-piperazinyl)-1-[2-(6-quinoxalinyloxy)ethyl]-2(1*H*)-pyrazinone,
- 1-{2-[3-(*N*,*N*-dimethylamino)phenoxy]ethyl}-3-(1-piperazinyl)-pyrazin-2(1*H*)-one,
- 3-(1-piperazinyl)-1-{2-[3-(trifluoromethyl)phenoxy]ethyl}-2(1*H*)-pyrazinone,
- 1-[2-(3-fluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3-nitrophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(3,5-difluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(phenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,6-difluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2-cyanophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-trifluoromethylphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-bromophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-{4-phenoxy-(phenoxy)}ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-fluorophenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-isopropylphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-{(4-allyl-2-methoxy)phenoxy}ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,6-difluorophenoxy)ethyl]-3-(3-methyl-1-piperazinyl)-2(1*H*)-pyrazinone,

- 1-[2-(4-trifluoromethylphenoxy)ethyl]-3-(3-methyl-1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(4-bromophenoxy)ethyl]-3-(3-methyl-1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-(2,4,5-trifluorobenzyl)-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[3-(2,4,5-trifluorophenyl)propyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-3-(1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,4,5-trifluorophenoxy)ethyl]-3-(4-*n*-butyl-1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,4,5-trifluorophenoxy)ethyl]-3-(4-methyl-1-piperazinyl)-2(1*H*)-pyrazinone,
- 1-[2-(2,4,5-trifluorophenoxy)ethyl]-3-(4-isopropyl-1-piperazinyl)-2(1*H*)-pyrazinone, and
- 1-[2-(3-benzoylphenoxy)ethyl]-3-(1-piperazinyl)-2(1*H*)-pyrazinone.

and their pharmacologically acceptable salts and solvates.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 as an active ingredient, together with a pharmaceutically acceptable carrier.

15. A method for the prophylaxis or treatment of a 5-HT_{2A} receptor-related disorder or condition comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 13.

16. The method according to claim 15 wherein the medical condition is selected from angina; Raynaud's phenomenon; intermittent claudication; coronary or peripheral vasospasms; hypertension; fibromyalgia; thrombotic illness including stroke; memory disorders, such as Alzheimer's disease; schizophrenia; obsessive-compulsive disorder; mood disorders; autism; anxiety disorders; depression disorders including depression with coexisting

diabetes; sexual function disorders; sleep disorders, such as insomnia; pain; substance abuse; extrapyramidal symptoms, e.g., associated with neuroleptic drug therapy using drugs, such as haloperidol and chlorpromazine; Parkinson's disease; glaucoma; urinary incontinence including urinary incontinence with co-existing diabetes; menopausal and post-menopausal hot flushes; bronchoconstriction disorders; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; diabetic complications, such as nephropathy, neuropathy and retinopathy.

17. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the prophylaxis or treatment of a 5-HT_{2A} receptor-related medical condition.

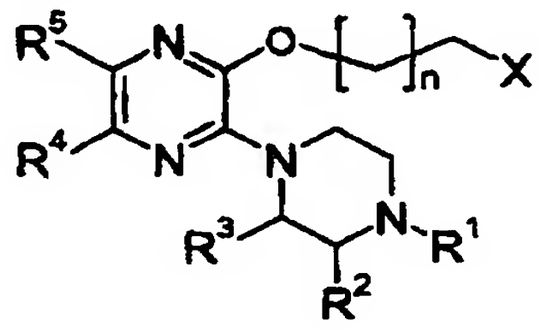
18. The use according to claim 17 wherein the medical condition is selected from angina; Raynaud's phenomenon; intermittent claudication; coronary or peripheral vasospasms; hypertension; fibromyalgia; thrombotic illness including stroke; memory disorders, such as Alzheimer's disease; schizophrenia; obsessive-compulsive disorder; mood disorders; autism; anxiety disorders; depression disorders including depression with coexisting diabetes; sexual function disorders; sleep disorders, such as insomnia; pain; substance abuse; extrapyramidal symptoms, e.g., associated with neuroleptic drug therapy using drugs, such as haloperidol and chlorpromazine; Parkinson's disease; glaucoma; urinary incontinence including urinary incontinence with co-existing diabetes; menopausal and post-menopausal hot flushes; bronchoconstriction disorders; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; diabetic complications, such as nephropathy, neuropathy and retinopathy.

19. The use of the compounds according to any one of claims 1 to13 as a diagnostic agent

20. A method of making a compound of formula (I) according to any one of claims 1 to 10 and 13,

wherein R^6 is selected from aryloxy, heteroaryloxy, arylthio, heteroarylthio, aryl-NH, r heteroaryl-NH,

by reacting a compound of the following formula (II):



(II)

wherein

X is OH;

R^1 is H, C_{1-6}-alkyl, aryl-C_1-C_3-alkyl, heteroaryl-C_1-C_3-alkyl, 2-hydroxyethyl, methoxy-C_2-C_4-alkyl, or C_1-C_4-alkoxycarbonyl; wherein

any aryl or heteroaryl residue may be substuted with C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy or cyano;

R^2 and R^3 each, independently, represent H or CH_3; and

R^4 and R^5 each, independently, represent H, halogen, methyl, or together with the ring, to which carbon atoms they are attached, form a 1*H*-quinoxalin-2-one nucleus;

with 1 to 10 molar equivalents of an appropriate phenol or thiophenol under Mitsunobu conditions, in the presence of diethyl azodicarboxylate (DEAD) or 1,1'-azobis(*N*,*N*-dimethylformamide (TMAD); and triphenylphosphine or tri-*n*-butylphosphine; in a solvent such as *N*,*N*-dimethylformamide (DMF), dichloromethane or tetrahydrofuran (THF), or in a suitable mixture of solvents, such as THF:DMF, at -25 to 50 °C, typically at room temperature, for 1-48 hours.

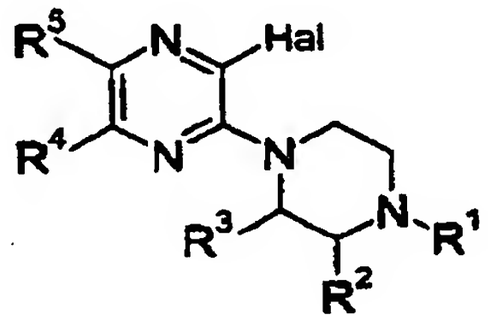
21. A method according to claim 20 for the preparation of compounds of formula (I) where R^1 is H, wherein R^1 in the corresponding intermediate of formula (II) is a protecting group selected from *tert*-butoxycarbonyl (*t*-BOC) or trityl.

22. A method according t any one of claim 20 or 21, wherein the intermediate of formula (II) is 2-[3-(4-*tert*-butoxycarbonyl-3-methyl-1-piperazinyl)-pyrazinyloxy]ethanol.

23. A method of preparing a compound of formula (I) according to any one of claims 1 to 13,

wherein R^6 is selected from aryloxy, heteroaryloxy, arylthio, heteroarylthio, aryl-NH, heteroaryl-NH, aryl or heteroaryl,

by reacting a compound of the following formula (IV),



(IV)

wherein

Hal is halogen;

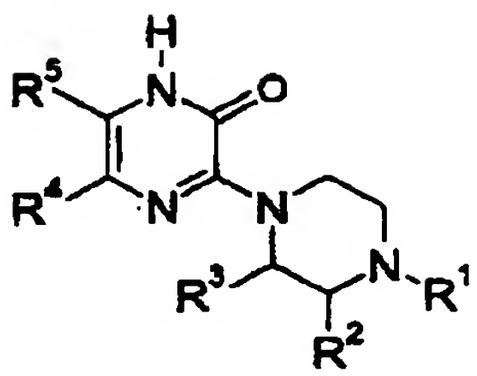
R^1 is H, C_{1-6}-alkyl, aryl-C_1-C_3-alkyl, heteroaryl-C_1-C_3-alkyl, 2-hydroxyethyl, methoxy-C_2-C_4-alkyl, or C_1-C_4-alkoxycarbonyl; wherein

any aryl or heteroaryl residue may be substuted with C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy or cyano;

R^2 and R^3 each, independently, represent H or CH_3; and

R^4 and R^5 each, independently, represent H, halogen, methyl, or together with the ring, to which carbon atoms they are attached, form a 1*H*-quinoxalin-2-one nucleus;

with an alkali metal or alkaline earth metal basic salt, in aqueous media, at 25 to 150 °C, to produce a compound of formula (V),



(V)

wherein

R^1 is H or C_{1-6}-alkyl, aryl-C_1-C_3-alkyl, heteroaryl-C_1-C_3-alkyl, 2-hydroxyethyl, methoxy-C_2-C_4-alkyl, or C_1-C_4-alkoxycarbonyl; wherein

any aryl or heteroaryl residue may be substuted with C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy or cyano;

R^2 and R^3 each, independently, represent H or CH_3; and

R^4 and R^5 each, independently, represent H, halogen, methyl, or together with the ring, to which carbon atoms they are attached, form a 1*H*-quinoxalin-2-one nucleus;

followed by N-alkylation of the compound of formula (V) by reaction with a compound of formula (VI),

$$R^6-CH_2-(CH_2)_n-Y \quad \text{(VI)}$$

wherein

n is 0, 1, 2, 3 or 4;

Y is a leaving group; and

R^6 represents aryloxy, heteroaryloxy, arylthio, heteroarylthio, aryl-NH, heteroaryl-NH, aryl, or heteroaryl; and

wherein any aryl or heteroaryl residue, alone or as part of another group, may be unsubstituted or substituted. Where substituted, one, two, three, four or five substituents may be present, preferably one or two for non-halogen substituents, and are independently selected from aryl, aryl-C_{1-2}-alkyl, arylcarbonyl, heteroaryl, heteroaryl-C_{1-2}-alkyl, heteroarylcarbonyl, aryloxy, heteroaryloxy, arylthio, heteroarylthio, arylamino, heteroarylamino, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyloxy, C_{3-6}-cycloalkylcarbonyl, C_{1-6}-alkyl, C_{2-6}-alkanoyl, C_{2-6}-alkynyl, C_{2-6}-alkenyl, or fluoro-C_{2-4}-alkyloxy, halogen,

trifluoromethyl, nitro, cyan , trifluoromethoxy, trifluoromethylthio, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino, C_{1-4}-dialkylamino, hydroxy or oxo;

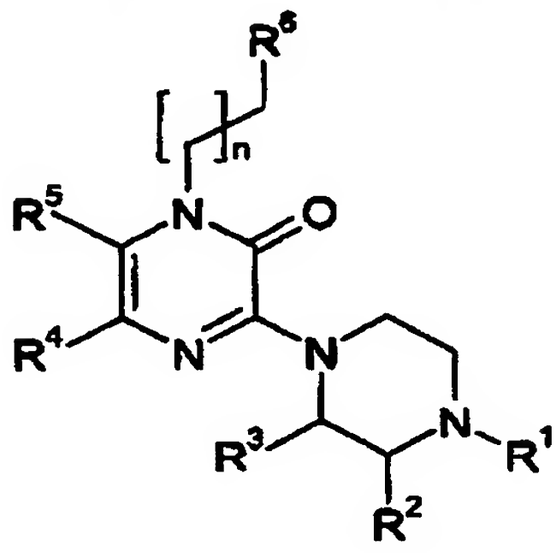
wherein any aryl or heteroaryl residue as substituents on aryl or heteroaryl, alone or as part of another group, in turn may be substituted in one or more positions, preferably one, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogen, trifluoromethyl, trifluoromethoxy, or cyano;

in the presence of a base in a suitable solvent at an elevated temperature.

24. A method according to claim 23 for the preparation of compounds of formula (I) where R^1 is H, wherein R^1 in the corresponding intermediate of formula (V) is a protecting group selected from tert-butoxycarbonyl (t-BOC) or trityl.

ABSTRACT

Compounds of the general formula (I):



(I)

wherein R^1, R^2, R^3 and R^4 are as described in the specification.

Further included are pharmaceutical compositions comprising the compounds, processes for their preparation, as well as the use of the compounds for the preparation of a medicament for the treatment of 5-HT_{2A} receptor-related medical conditions.